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# BMJ Open

## Fatty liver index is associated with albuminuria and chronic kidney disease: a real-world evidence study

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**1 Fatty liver index is associated with albuminuria and chronic kidney**  
**2 disease: a real-world evidence study**

**3**  
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## **Statement of authorship**

All authors believe that the manuscript represents valid work and have reviewed and approved the final version. The work has not been published previously, and not under consideration for publication elsewhere, in part or in whole.

## **The author contribution lists**

Conceived and designed the experiments: Y. L. and K. S.

Performed the experiments: F. L., Y. Q., W. F., C. C., K. S. and D. L.

Analyzed the data: K. S. and M. R.

Wrote the manuscript: K.S. and D. L.

## **Data Sharing Statement**

The work described was original research that has not been published previously, and not under consideration for publication elsewhere, in part or in whole. All authors believe that the manuscript represents valid work and have reviewed and approved the final version. Main document data and additional unpublished data from the study are available by sending Email to lizyhenu@163.com with proper purposes.

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59 **Conflict of interests**

60 The authors have declared that no competing interests exist.

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64 **ABSTRACT**

65 **Objectives:** The effects of lipid metabolism disorder on the renal damage have drawn  
66 much attention. By using the fatty liver index (FLI) as a validated indicator of hepatic  
67 steatosis, this study aims at provide insight about the possible links between fatty liver  
68 and development of chronic kidney disease (CKD).

69 **Setting:** level of care: primary.

70 **Participants:** We performed a population-based study in 9,436 subjects aged 40 years  
71 or older.

72 **Primary and secondary outcome measures:** FLI is calculated by using an algorithm  
73 based on body mass index (BMI), waist circumference (WC), triglycerides (TG) and  
74  $\gamma$ -glutamyltransferase ( $\gamma$ -GGT). Increased urinary albumin excretion was defined  
75 according to the urinary albumin-to-creatinine ratio ranges greater or equal than 30  
76 mg/g. CKD was defined as estimated glomerular filtration rate (eGFR) less than 60  
77 mL/min per 1.73 m<sup>2</sup> or presence of albuminuria.

78 **Results:** There were 620 (6.6%) subjects categorized as increased urinary albumin  
79 excretion and 753 (8.0%) subjects categorized as CKD. Participants with higher FLI  
80 had increased age, blood pressure, low-density lipoprotein cholesterol, fasting plasma  
81 glucose, fasting insulin and decreased eGFR level. Prevalence of increased urinary  
82 albumin excretion and CKD tended to increase with the elevated FLI quartiles. In  
83 logistic regression analysis, compared with subjects in the lowest quartile of FLI, the  
84 adjusted odds ratios (ORs) in the highest quartile was 2.30 [95% confidence interval

(CI), 1.36 - 3.90] for increased urinary albumin excretion and 1.93 (95% CI, 1.18 - 3.15) for CKD.

**Conclusion:** Hepatic steatosis evaluating by FLI is independently associated with increased urinary albumin excretion and prevalence of CKD in middle-aged and elderly Chinese.

**Keywords:** Fatty liver index; Hepatic steatosis; Increased urinary albumin excretion; Chronic kidney disease

95

## 96 Introduction

97 As directly affects the global burden of cardiovascular disease mortality, chronic  
98 kidney disease (CKD) has become one of the leading public health problem  
99 world-wide <sup>1</sup>. The most recent national survey in 2012 reported that the prevalence of  
100 CKD was 10.8%, representing an estimated 119.5 million patients in China with  
101 chronic kidney damage <sup>2</sup>. In addition to CKD, an increasing number of studies have  
102 provided substantial evidence of albuminuria as a risk factor for future cardiovascular  
103 events <sup>3</sup>. Both renal and cardiovascular diseases sharing similar traditional risk factors,  
104 such as lipid metabolism disorder, which could have particularly broad implications  
105 for the outcome of cardiovascular morbidity and mortality.

106 Association of hepatic steatosis with CKD development and its impact on the  
107 reduction of the estimated glomerular filtration rate (eGFR) have been extensively  
108 investigated over the past decade <sup>4</sup>. The substantial evidence linked hepatic steatosis  
109 to the increased risk and severity of CKD, which may be a target for the prevention  
110 and treatment of the disease <sup>5</sup>. As a convenient scoring system for the presence of  
111 hepatic lipid deposits, the fatty liver index (FLI) is a surrogate steatosis biomarker  
112 developed in a cohort of patients from the general population <sup>6</sup>. Compared with other  
113 techniques for evaluating hepatic steatosis, FLI is simple to obtain as body mass index  
114 (BMI), waist circumference (WC), triglycerides (TG) and  $\gamma$ -glutamyltransferase  
115 ( $\gamma$ -GGT) are routine measurements in clinical practice. Previous studies have  
116 demonstrated that FLI could determine fatty liver disease, incident type 2 diabetes and

117 incident hypertension with considerable accuracy<sup>6-8</sup>. Moreover, FLI is associated with  
118 insulin resistance early atherosclerosis and risk of coronary heart disease, which could  
119 help physicians early detect subjects of greater cardiovascular risk and select patients  
120 for intensified lifestyle counseling<sup>9 10</sup>.

121 Clarified the association of FLI with albuminuria and prevalent CKD would  
122 probably shed light on the prevention and preemptive treatment of related diseases.  
123 Recently, a cross-sectional study was conducted to investigate the association between  
124 FLI and CKD by recruiting adults undergoing a health check-up<sup>11</sup>. However, by  
125 including only 731 subjects, the study did not evaluate the association between FLI  
126 and albuminuria, either. Therefore, we analyzed data from a community-based  
127 Chinese population to comprehensively look into the relationship of FLI with both  
128 increased urinary albumin excretion and CKD.

129  
130 **Subjects and methods**

131 **Study population and design**

132 We performed a cross-sectional study in a community in Guangzhou, China from  
133 June to November, 2011. The study population was from the REACTION study and  
134 details of this study have been published previously<sup>12-14</sup>. During the recruiting phase,  
135 a total of 10,104 residents aged 40 years or older were invited to participate by  
136 examination notices or home visits. In total, 9,916 subjects signed the consent form  
137 and agreed to participate in the survey, and the participation rate was 98.1%. The  
138 subjects who failed to provided information (BMI: n=206; WC: n=62; TG: n=23;

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4 139  $\gamma$ -GGT: n=38; or urinary albumin-to-creatinine ratio [ACR]: n=149) were excluded  
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6 140 from the analyses. Accordingly, a total of 9,438 eligible individuals were included in  
7  
8 141 the final data analyses. The study protocol was approved by the Institutional Review  
9  
10 142 Board of the Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University and  
11  
12 143 was in accordance with the principle of the Helsinki Declaration II. Written informed  
13  
14 144 consent was obtained from each participant before data collection.  
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#### 18 145 **Clinical and biochemical measurements**

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20 146 We collected information on lifestyle factors, sociodemographic characteristics  
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22 147 and family history by using a standard questionnaire. Smoking or drinking habit was  
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24 148 classified as 'never', 'current' (smoking or drinking regularly in the past 6 months) or  
25  
26 149 'ever' (cessation of smoking or drinking more than 6 months)<sup>15</sup>. A short form of the  
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28 150 International Physical Activity Questionnaire (IPAQ) was used to estimate physical  
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30 151 activity at leisure time by adding questions on frequency and duration of moderate or  
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32 152 vigorous activities and walking<sup>16</sup>. Separate metabolic equivalent hours per week  
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34 153 (MET-h/week) were calculated for evaluation of total physical activity.  
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39 154 All participants completed anthropometrical measurements with the assistance of  
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41 155 trained staff by using standard protocols. Three times consecutively blood pressure  
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43 156 measurements by the same observer with a 5-minute interval were obtained by an  
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45 157 automated electronic device (OMRON, Omron Company, China). The average of  
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47 158 three measurements of blood pressure was used for analysis. Body height and body  
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49 159 weight were recorded to the nearest 0.1 cm and 0.1 kg while participants were  
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51 160 wearing light indoor clothing without shoes. BMI was calculated as weight in  
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161 kilograms divided by height in meters squared ( $\text{kg/m}^2$ ). Obesity was defined as BMI  
162 equal or greater than 28 and overweight was defined as BMI equal or greater than 24  
163 and less than 28. WC was measured at the umbilical level with participant in standing  
164 position, at the end of gentle expiration.

165 Venous blood samples were collected for laboratory tests after an overnight  
166 fasting of at least 10 hours. Measurement of fasting plasma glucose (FPG), fasting  
167 serum insulin, TG, total cholesterol (TC), high-density lipoprotein cholesterol  
168 (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine,  $\gamma$ -GGT, aspartate  
169 aminotransferase (AST) and alanine aminotransferase (ALT) was done using an  
170 autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA).

171 As surrogate marker of hepatic steatosis, FLI was analyzed based on BMI, WC,  
172 TG, and  $\gamma$ -GGT, which has been validated against liver ultrasound in the general  
173 population and has been proven accurate in detecting fatty liver<sup>6 10</sup>. FLI is calculated  
174 as: 
$$\text{FLI} = \left( e^{0.953 * \log_e(\text{TG}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{GGT}) + 0.053 * \text{WC} - 15.745} \right) / \left( 1 + e^{0.953 * \log_e(\text{TG}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{GGT}) + 0.053 * \text{WC} - 15.745} \right) * 100$$
. The  
175  
176 abbreviated Modification of Diet in Renal Disease (MDRD) formula recalibrated for  
177 Chinese population was used to calculate estimated glomerular filtration rate (GFR)  
178 expressed in mL/min per  $1.73 \text{ m}^2$  using a formula of  $\text{eGFR} = 175 \times [\text{serum creatinine}$   
179  $\times 0.011]^{-1.234} \times [\text{age}]^{-0.179} \times [0.79 \text{ if female}]$ , where serum creatinine was expressed as  
180  $\mu\text{mol/L}$ <sup>17</sup>. Diabetes was diagnosed according to the 1999 World Health Organization  
181 diagnostic criteria<sup>18</sup>.

182 **Definition of increased urinary albumin excretion and chronic kidney disease.**

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4 183 Definitions of abnormalities in albumin excretion were according to the latest  
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6 184 guidelines of American Diabetes Association's Standards of Medical Care <sup>19</sup>. The first  
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8 185 morning spot urine samples were collected for assessing the ACR. Urine albumin and  
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11 186 creatinine were measured by chemiluminescence immunoassay (Siemens Immulite  
12  
13 187 2000, United States) and the Jaffe's kinetic method (Biobase-Crystal, Jinan, China)  
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15  
16 188 on the automatic analyzer, respectively. ACR was calculated by dividing the urinary  
17  
18 189 albumin concentrations by the urinary creatinine concentrations and expressed in  
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21 190 mg/g. Increased urinary albumin excretion was defined according to the ACR ranges  
22  
23 191 greater or equal than 30 mg/g. Chronic kidney disease (CKD) was defined as eGFR  
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26 192 less than 60 mL/min per 1.73 m<sup>2</sup> or presence of albuminuria (ACR greater or equal  
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28 193 than 30 mg/g).

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### 32 33 195 **Statistical analysis**

34  
35 196 Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary,  
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37  
38 197 NC, USA). Continuous variables were presented as means  $\pm$  standard deviation (SD)  
39  
40 198 except for skewed variables, which were presented as medians (interquartile ranges).  
41  
42  
43 199 Categorical variables were expressed as numbers (proportions). FLI, FPG, TG, ALT,  
44  
45 200 AST,  $\gamma$ -GGT and MET-h/week were logarithmically transformed before analysis due  
46  
47  
48 201 to a non-normal distribution. FLI was presented as quartiles and linear regression  
49  
50 202 analysis was used to test for trend across groups. Differences among groups were  
51  
52 203 tested by one-way ANOVA and *post hoc* comparisons were performed by using  
53  
54  
55 204 Bonferroni correction. Comparisons between categorical variables were performed

205 with the  $\chi^2$  test.

206 Pearson's correlations were performed to test the correlations between FLI and  
207 the risk factors for kidney disease. Variables significant at  $P < 0.20$  in Pearson's  
208 correlations were put into the multivariate stepwise linear regression models to  
209 identify factors that independently associated with FLI. We analyzed the impact of  
210 FLI on the prevalence of increased urinary albumin excretion and CKD. The  
211 unadjusted and multivariate-adjusted logistic regression analysis was used to assess  
212 the risk of prevalent increased urinary albumin excretion and CKD in relation to each  
213 quartile increase in FLI level. Variables considered as potential covariates and  
214 significant in the stepwise linear regression were put into multivariate-adjusted  
215 logistic regression analysis. Model 1 is unadjusted. Model 2 is adjusted for age. Model  
216 3 is adjusted for age, sex, BMI, WC, current smoking status, current drinking status,  
217 physical activity, SBP, DBP, TG, LDL-C, fasting insulin, ALT, AST and  $\gamma$ -GGT. Odds  
218 ratios (OR) and the corresponding 95% confidence intervals (95% CI) were calculated.  
219 Relationship of FLI level with albuminuria and CKD were also explored in subgroups  
220 stratified by gender (men/women), age ( $\geq 60$ / $< 60$  years), degree of obesity  
221 (normal/overweight/obesity), current smoking (yes/no), current drinking (yes/no),  
222 hypertension (yes/no) and diabetes (yes/no). Tests for interaction were performed with  
223 including simultaneously each strata factor, the quartiles of FLI level and the  
224 respective interaction terms (strata factor multiplied by quartiles of FLI level) in the  
225 models.

226 All statistical tests were two-sided, and a  $P$  value  $< 0.05$  was considered

227 statistically significant.

228

## 229 **Results**

### 230 **Clinical characteristics of the study population**

231 Among the 9,436 enrolled individuals, the mean age was  $55.9 \pm 8.0$  years. The  
232 median FLI was 19.1 with interquartile range 8.6 to 37.4. There were 620 (6.6%)  
233 subjects categorized as increased urinary albumin excretion and 753 (8.0%) subjects  
234 categorized as CKD, respectively. Table 1 shows the clinical and biochemical  
235 characteristics of the participants according to FLI quartiles. Participants with higher  
236 FLI level had elevated age, BMI, WC, SBP, DBP, TG, TC, LDL-C, FPG, fasting  
237 insulin, ALT, AST,  $\gamma$  - GGT and higher proportions of current smokers and current  
238 drinkers (all P for trend  $< 0.0001$ ). Those with higher FLI level also associated with  
239 decreased HDL-C and eGFR (all P for trend  $< 0.0001$ ).

### 240 **Associations between FLI and metabolic risk factors**

241 Analysis of Pearson's correlation showed that age, sex, BMI, WC, SBP, DBP, TG,  
242 TC, HDL-C, LDL-C, FPG, fasting insulin, ALT, AST,  $\gamma$ -GGT and eGFR were  
243 significantly correlated with FLI level. Further multivariate stepwise linear regression  
244 showed that age, sex, BMI, WC, SBP, DBP, TG, LDL-C, fasting insulin, ALT, AST  
245 and  $\gamma$ -GGT were independent determinants for FLI level (Table 2).

### 246 **Associations of FLI with increased urinary albumin excretion and CKD**

247 As shown in Figure.1A, from the lowest quartile to the highest quartile of FLI  
248 level, the prevalence of increased urinary albumin excretion was 3.64%, 4.83%,

6.23% and 11.57%, respectively (P for trend < 0.0001). Strikingly, the prevalence of CKD also tended to increase with the elevated FLI quartile (Figure.1B, P for trend < 0.0001). As shown in Table 3, compared with participants in quartile 1 of FLI, univariate logistic regression analysis showed that participants in quartile 2, quartile 3 and quartile 4, respectively, have a significant correlation with increased odds of increased urinary albumin excretion and CKD (all P for trend < 0.0001). In multivariate logistic regression analyses (Model 3), the ORs of increased urinary albumin excretion for increasing FLI quartiles were 1.00 (reference), 0.96 (95% CI 0.66 - 1.39), 1.17 (95% CI 0.77 - 1.77) and 2.30 (95% CI 1.36 - 3.90). Similarly, the ORs of CKD for increasing FLI quartiles in Model 3 were 1.00 (reference), 1.00 (95% CI 0.71 - 1.40), 1.03 (95% CI 0.70 - 1.51) and 1.93 (95% CI 1.18 - 3.15), respectively (Table 3).

**Subgroups analysis of FLI with increased urinary albumin excretion and CKD**

As shown in Figure. 2 & 3, the associations of FLI level with increased urinary albumin excretion and CKD were not consistently the same in subgroups analyses. Significant relationship of FLI level with both increased urinary albumin excretion and CKD were detected in women, younger subjects (age less than 60 years), overweight subjects, non-current smokers, non-current drinkers and in those with hypertension or with diabetes (all P < 0.05). In the subgroups analysis, no statistically significance of interaction term between quartiles of FLI and each strata factor was detected.

## 271 Discussion

272 We evaluated the association between hepatic steatosis and kidney disease in a  
273 large population of middle-age Chinese subjects from the REACTION study.  
274 Presence of fatty liver assessed by FLI was associated with increased urinary albumin  
275 excretion and reduction of the eGFR in the present study. The association was  
276 independent of potential confounding risk factors. To our current knowledge, this is  
277 the largest population-based study to explore the association of FLI with both  
278 albuminuria and CKD. Early intervention is of great importance for albuminuria and  
279 CKD, the present findings may just give insights into lipid metabolism for prevention  
280 and early detection of the diseases.

281 The best method for an accurate assessment and diagnosis of hepatic steatosis is  
282 histologic analysis of biopsies<sup>20</sup>. However, it is uneconomical to conduct liver  
283 biopsies especially by the fact of our large sample population. Hepatic ultrasonic  
284 examination is widely used in clinical practice and epidemiological studies in  
285 detecting fatty infiltration of the liver<sup>21 22</sup>. However, the noninvasive technique is not  
286 sensitive enough to detect mild steatosis and does not allow precise quantification of  
287 severity of fatty degeneration in hepatic tissue<sup>23</sup>. As another surrogate marker of  
288 histological fatty liver, FLI is defined as the accumulation of excessive liver fat<sup>24</sup>.  
289 Based on the former researches, FLI has been proven accurate in detecting fatty liver  
290 against liver ultrasound and demonstrating the presence of hepatic fat against  
291 magnetic resonance spectroscopy<sup>6 9 10</sup>. The superiority of this non-invasive  
292 assessment techniques is that a higher score will indicate a higher rate of liver fatty

293 degeneration. However, optimal cut-off point of the FLI for evaluating liver fatty  
294 infiltration should be considered as it varied according to the study population <sup>25 26</sup>.  
295 Through the results of our research in Chinese subjects, further studies are therefore  
296 needed to externally discuss the optimal cut-off point of the FLI for predicting hepatic  
297 steatosis.

298       Detection and prevention of kidney disease progression and urinary albumin  
299 excretion is difficult to process in the early stage. Dyslipidemia is increasingly  
300 recognized as important pathogenic mechanism in deterioration of renal function.  
301 Recently, we conducted a clinical investigation to assess the associations of routine  
302 lipid measures with kidney disease in the same cohort. In the study, discordant  
303 associations of lipid parameters with renal insufficiency was detected while TG to  
304 HDL-C ratio is a better marker for evaluating increased urinary albumin excretion and  
305 CKD <sup>27</sup>. As one of the phenotype of dyslipidemia, the pathogeneses of hepatic  
306 steatosis is closely related to kidney disease with regard to insulin resistance and  
307 chronic inflammation <sup>28</sup>. Hepatokines, which are proteins secreted by hepatocytes,  
308 have been found to link to the induction of metabolic phenotypes through inter-organ  
309 communication based on recent studies <sup>29</sup>. Because of the high prevalence and burden  
310 of the fatty liver disease, it is important to identify which patients are most likely to be  
311 exposed to early stage renal injury <sup>30</sup>. Consequently, we closely monitor the  
312 association of the hepatic steatosis predict by FLI with prevalent increased urinary  
313 albumin excretion and CKD.

314       Consistent with our findings, a previous study reported that hepatic steatosis

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4 315 evaluated by FLI might contribute to CKD development <sup>11</sup>. Elevated albuminuria is  
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6 316 well known to be associated with increased risk for early diabetes renal damage,  
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8 317 however, the identification and classification of kidney disease was assessed only by  
9  
10 318 eGFR in that study. Moreover, 731 adults that underwent routine health evaluations  
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12  
13 319 were included in that study and the small sample size cannot better represent the  
14  
15 320 whole population. By totally including 9,438 subjects and adopting both albuminuria  
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17 321 and eGFR for renal damage assessment, the data in our study demonstrated that the  
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19 322 FLI is associated with kidney disease, which might be an efficient screening indicator  
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21 323 for the early prevention of related diseases.  
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25 324 Some limitations of the study must be noted. Firstly, owing to the observational  
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27 325 design of the current study, we should cautiously interpret the present findings as no  
28  
29 326 causal inference can be drawn. Further prospective studies are therefore needed to  
30  
31 327 determine the precise relationship between FLI and risk of renal diseases. Secondly,  
32  
33 328 by including only Chinese subjects, the results of the present study might not be  
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35 329 representative of other ethnic groups, especially for those in the developed or  
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37 330 undeveloped countries. To some extent, however, the present study of Chinese  
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39 331 population was still a convenience sample and selection bias is inevitable. Thirdly,  
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41 332 when evaluating the findings of the present study, the results should be interpreted  
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43 333 cautiously due to possible bias from using the indirect indicator FLI to assess fatty  
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45 334 liver disease. Moreover, the internal accuracy of FLI for evaluation hepatic steatosis  
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47 335 should also be validated by using other techniques, before it can be employed for  
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49 336 these purposes. Fourthly, we observed that FLI seem to play a different efficiency for  
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337 kidney disease assessment in different stratifications. For example, a significant  
338 association of FLI with increased urinary albumin excretion and CKD only in subjects  
339 without current alcohol consumption. To better discriminate alcoholic fatty liver  
340 disease and non-alcoholic fatty liver disease, further studies need to clearly described  
341 the precise exposure of alcohol use by collecting histories of alcohol intake in a  
342 quantitative manner. Fifthly, although a spectrum of covariates was included in the  
343 adjustment, other potential mediators such as daily energy and protein intake and  
344 medicine that influence the renin-angiotensin-system of the subjects, should also be  
345 considered in the present study.

346 In conclusion, by including a large population based cohort, the present study  
347 provides evidence that increased FLI is independently associated with prevalence of  
348 albuminuria and CKD. Further prospective studies are necessary to verify our  
349 findings in external populations.

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352

353 **Figure legends**

354

355 **Figure. 1** Prevalence of increased urinary albumin excretion and CKD in different quartiles of  
356 FLI levels. (A) Increased urinary albumin excretion. (B) CKD.

357

358 **Figure. 2** Risk of prevalent increased urinary albumin excretion with each quartile increase of  
359 FLI levels in different subgroups.

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361 **Figure. 3** Risk of prevalent CKD with each quartile increase of FLI levels in different  
362 subgroups.

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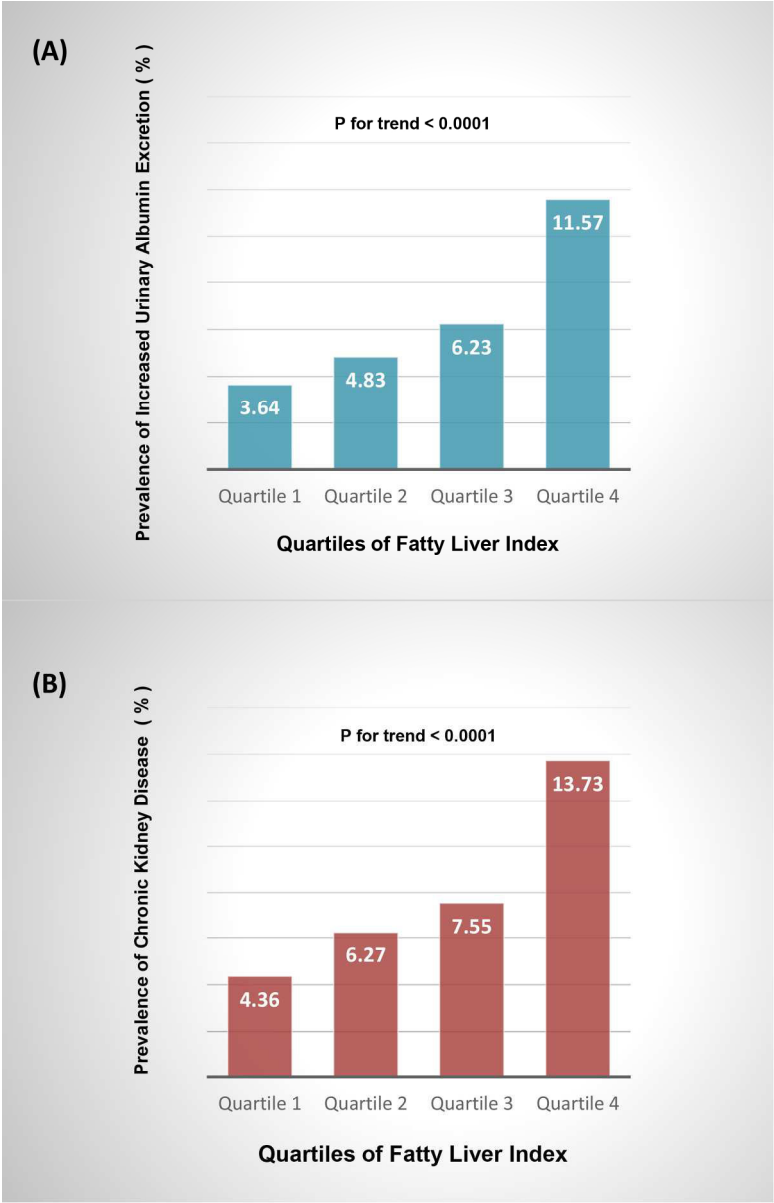
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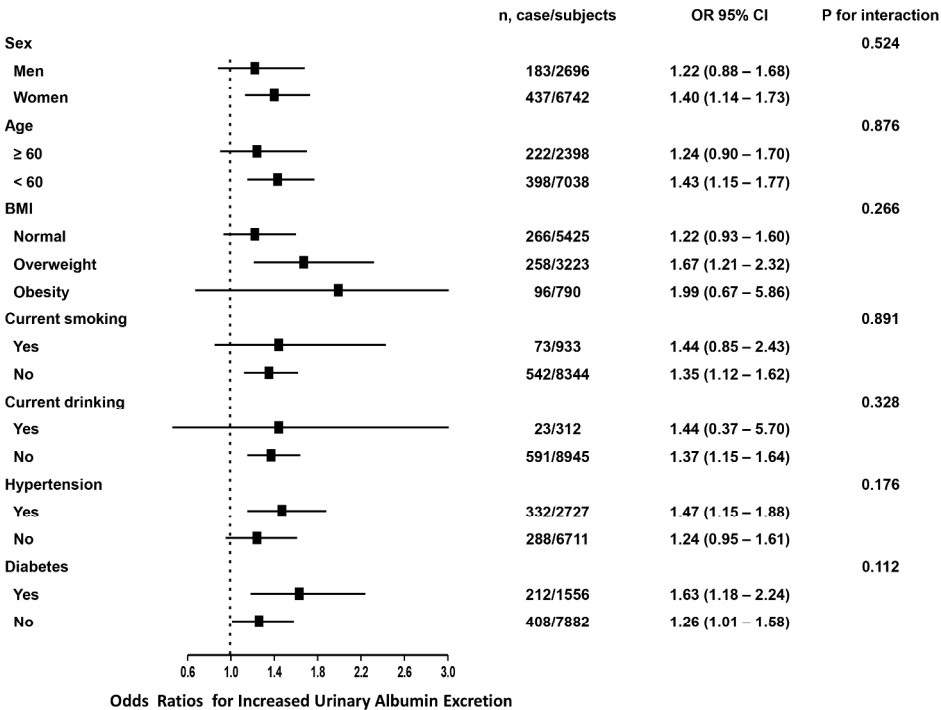
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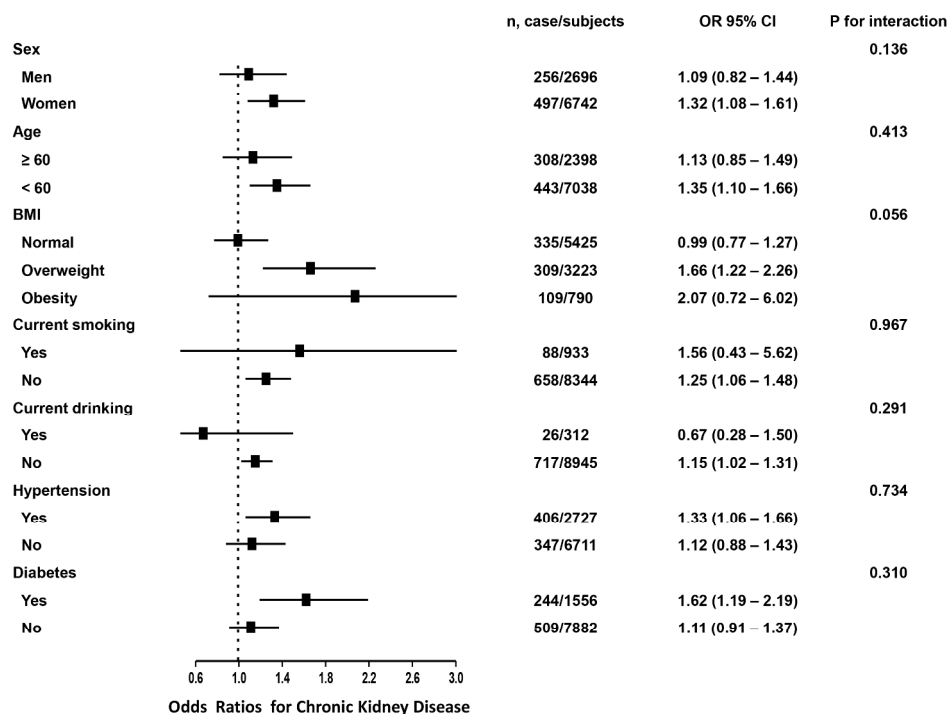
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145x226mm (300 x 300 DPI)



254x190mm (300 x 300 DPI)



254x190mm (300 x 300 DPI)

<b>Table 1.</b> Characteristics of study population by FLI quartiles					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
n (%)	2360 (25.01)	2359 (24.99)	2359 (24.99)	2360 (25.01)	
Fatty liver index	5.00 (3.27 – 6.74)	13.23 (10.76 – 15.99)	26.96 (22.74 – 31.75)	54.71 (45.40 – 68.10)	
Urinary albumin to creatinine ratio (mg/g)	7.65 (5.59 – 11.12)	8.01 (5.64 – 11.71)	8.06 (5.73 – 11.83)*	8.93 (5.96 – 15.01)*	< 0.0001
Age (years)	54.3 ± 7.8	55.8 ± 7.9*	56.5 ± 7.9*	56.9 ± 8.3*	< 0.0001
Male [n (%)]	427 (18.09)	593 (25.17)	701 (29.72)	975 (41.31)	< 0.0001
BMI (kg/m <sup>2</sup> )	20.6 ± 2.0	22.9 ± 2.0*	24.4 ± 2.1*	26.8 ± 3.5*	< 0.0001
WC (cm)	72.0 ± 5.8	79.3 ± 5.4*	84.1 ± 5.5*	91.3 ± 8.5*	< 0.0001
SBP (mmHg)	118.6 ± 14.7	124.5 ± 15.9*	128.4 ± 15.8*	132.5 ± 16.1*	< 0.0001
DBP (mmHg)	71.2 ± 9.1	74.2 ± 9.3*	76.5 ± 9.4*	79.3 ± 9.8*	< 0.0001
Current smoking [n (%)]	169 (7.3)	202 (8.7)	227 (9.8)	335 (14.4)	< 0.0001
Current drinking [n (%)]	57 (2.5)	70 (3.0)	68 (2.9)	117 (5.1)	< 0.0001
TG (mmol/L)	0.85 (0.69 – 1.07)	1.12 (0.90 – 1.43)*	1.49 (1.13 – 1.94)*	2.10 (1.56 – 3.01)*	< 0.0001
TC (mmol/L)	4.79 ± 1.24	5.16 ± 1.22*	5.35 ± 1.13*	5.54 ± 1.17*	< 0.0001
HDL-C (mmol/L)	1.45 ± 0.41	1.37 ± 0.35*	1.29 ± 0.31*	1.19 ± 0.28*	< 0.0001

LDL-C (mmol/L)	2.82 ± 0.90	3.19 ± 0.94*	3.31 ± 0.91*	3.28 ± 0.95*	< 0.0001
FPG (mmol/L)	5.23 (4.89 – 5.61)	5.33 (4.95 – 5.80)*	5.47 (5.05 – 5.96)*	5.73 (5.23 – 6.42)*	< 0.0001
Fasting insulin (μIU/ml)	5.10 (3.90 – 6.50)	6.50 (5.00 – 8.40)*	7.90 (6.10 – 10.30)*	10.50 (7.80 – 13.70)*	< 0.0001
ALT (U/L)	10.0 (8.0 – 14.0)	12.0 (9.0 – 16.0)*	13.0 (10.0 – 17.0)*	17.0 (12.0 – 24.0)*	< 0.0001
AST (U/L)	17.0 (14.0 – 20.0)	18.0 (15.0 – 21.0)*	18.0 (15.0 – 22.0)*	20.0 (17.0 – 25.0)*	< 0.0001
γ-GGT (U/L)	14.0 (11.0 – 17.0)	18.0 (14.0 – 23.0)*	22.0 (17.0 – 29.0)*	31.0 (23.0 – 47.0)*	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	108.0 ± 25.4	102.5 ± 23.7*	99.9 ± 19.6*	95.5 ± 19.5*	< 0.0001
Physical activity (MET-h/week)	24.0 (10.5 – 49.0)	24.0 (10.5 – 45.0)	23.0 (10.5 – 42.0)	21.0 (10.5 – 42.0)*	0.006
<p>1. Data were means ± SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.</p> <p>2. P for trend was calculated for the linear regression analysis tests across the groups. P values were for the ANOVA or <math>\chi^2</math> analyses across the groups.</p> <p>3. *P &lt; 0.05 compared with Quartile 1 of fatty liver index.</p> <p>4. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyltransferase; eGFR, estimated glomerular filtration rate.</p>					

Table 2. Pearson’s correlation and stepwise regression analysis of determinants of FLI				
	r	P value	Standardized $\beta$	P value
Age (years)	0.12	< 0.0001	0.01	0.010
Sex (men=1, women=2)	-0.19	< 0.0001	-0.04	< 0.0001
BMI (kg/m <sup>2</sup> )	0.71	< 0.0001	0.30	< 0.0001
WC (cm)	0.78	< 0.0001	0.42	< 0.0001
Physical activity (MET-h/week)	-0.02	0.060	-	-
SBP (mmHg)	0.32	< 0.0001	0.01	0.006
DBP (mmHg)	0.32	< 0.0001	0.01	0.047
TG (mmol/L)	0.68	< 0.0001	0.42	< 0.0001
HDL-C (mmol/L)	-0.26	< 0.0001	-	-
LDL-C (mmol/L)	0.21	< 0.0001	0.06	< 0.0001
FPG (mmol/L)	0.22	< 0.0001	-	-
Fasting insulin ( $\mu$ IU/ml)	0.40	< 0.0001	0.01	0.0002
ALT (U/L)	0.20	< 0.0001	0.05	< 0.0001
AST (U/L)	0.15	< 0.0001	-0.03	< 0.0001
$\gamma$ -GGT (U/L)	0.35	< 0.0001	0.16	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	-0.19	< 0.0001	-	-

r, correlation coefficient;  $\beta$ , regression coefficient.

**Table 3.** The risk of prevalent albuminuria and CKD according to quartiles of FLI

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Increased urinary albumin excretion	Model 1	1	1.34 (1.01 – 1.79)	1.76 (1.34 – 2.31)	3.46 (2.70 – 4.44)	< 0.0001
	Model 2	1	1.29 (0.97 – 1.72)	1.66 (1.27 – 2.19)	3.25 (2.53 – 4.17)	< 0.0001
	Model 3	1	0.96 (0.66 – 1.39)	1.17 (0.77 – 1.77)	2.30 (1.36 – 3.90)	0.001
CKD	Model 1	1	1.47 (1.13 – 1.90)	1.79 (1.39 – 2.30)	3.49 (2.77 – 4.39)	< 0.0001
	Model 2	1	1.39 (1.07 – 1.80)	1.65 (1.28 – 2.12)	3.16 (2.51 – 3.99)	< 0.0001
	Model 3	1	1.00 (0.71 – 1.40)	1.03 (0.70 – 1.51)	1.93 (1.18 – 3.15)	0.012

Data are odds ratios (95% confidence interval). Participants without increased urinary albumin excretion or CKD are defined as 0 and with increased urinary albumin excretion or CKD as 1.

Model 1 is unadjusted.

Model 2 is adjusted for age.

Model 3 is adjusted for age, sex, BMI, WC, current smoking status, current drinking status, physical activity, SBP, DBP, TG, LDL-C, fasting insulin, ALT, AST and  $\gamma$ -GGT.

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## Fatty liver index is associated with albuminuria and chronic kidney disease: a population-based study

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**Fatty liver index is associated with albuminuria and chronic kidney disease: a population-based study**

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## **Statement of authorship**

All authors believe that the manuscript represents valid work and have reviewed and approved the final version. The work has not been published previously, and not under consideration for publication elsewhere, in part or in whole.

## **The author contribution lists**

Conceived and designed the experiments: Y. L. and K. S.

Performed the experiments: F. L., Y. Q., W. F., C. C., K. S. and D. L.

Analyzed the data: K. S. and M. R.

Wrote the manuscript: K.S. and D. L.

## **Data Sharing Statement**

The work described was original research that has not been published previously, and not under consideration for publication elsewhere, in part or in whole. All authors believe that the manuscript represents valid work and have reviewed and approved the final version. Main document data and additional unpublished data from the study are available by sending Email to lizyhenu@163.com with proper purposes.

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60

61 **Conflict of interests**

62 The authors have declared that no competing interests exist.

63

64

65

66 **ABSTRACT**

67 **Objectives:** The effects of lipid metabolism disorder on the renal damage have drawn  
68 much attention. By using the fatty liver index (FLI) as a validated indicator of hepatic  
69 steatosis, this study aims at provide insight about the possible links between fatty liver  
70 and development of chronic kidney disease (CKD).

71 **Setting:** hospital.

72 **Participants:** We performed a population-based study in 9,436 subjects aged 40 years  
73 or older.

74 **Primary and secondary outcome measures:** FLI is calculated by using an algorithm  
75 based on body mass index (BMI), waist circumference (WC), triglycerides (TG) and  
76  $\gamma$ -glutamyltransferase ( $\gamma$ -GGT). Increased urinary albumin excretion was defined  
77 according to the urinary albumin-to-creatinine ratio ranges greater or equal than 30  
78 mg/g. CKD was defined as estimated glomerular filtration rate (eGFR) less than 60  
79 mL/min per 1.73 m<sup>2</sup> or presence of albuminuria.

80 **Results:** There were 620 (6.6%) subjects categorized as increased urinary albumin  
81 excretion and 753 (8.0%) subjects categorized as CKD. Participants with higher FLI  
82 had increased age, blood pressure, low-density lipoprotein cholesterol, fasting plasma  
83 glucose, fasting insulin and decreased eGFR level. Prevalence of increased urinary  
84 albumin excretion and CKD tended to increase with the elevated FLI quartiles. In  
85 logistic regression analysis, compared with subjects in the lowest quartile of FLI, the  
86 adjusted odds ratios (ORs) in the highest quartile was 2.30 [95% confidence interval

(CI), 1.36 - 3.90] for increased urinary albumin excretion and 1.93 (95% CI, 1.18 - 3.15) for CKD.

**Conclusion:** Hepatic steatosis evaluating by FLI is independently associated with increased urinary albumin excretion and prevalence of CKD in middle-aged and elderly Chinese.

**Keywords:** Fatty liver index; Hepatic steatosis; Increased urinary albumin excretion; Chronic kidney disease

**Strengths and Limitations**

1. The study was performed in a large population-based cohort in 9,436 Chinese subjects.
2. Findings of the study may be applied to the majority of patients in general practice with suspected hepatic steatosis.
3. Results should be interpreted cautiously due to the observational design of the current study.

## 104 Introduction

105 As directly affects the global burden of cardiovascular disease mortality, chronic  
106 kidney disease (CKD) has become one of the leading public health problem  
107 world-wide <sup>1</sup>. Recent national survey conducted between 2007 and 2010 reported that  
108 the prevalence of CKD was 10.8%, representing an estimated 119.5 million patients in  
109 China with chronic kidney damage <sup>2</sup>. In addition to CKD, an increasing number of  
110 studies have provided substantial evidence of albuminuria as a risk factor for future  
111 cardiovascular events <sup>3</sup>. Both renal and cardiovascular diseases sharing similar  
112 traditional risk factors, such as lipid metabolism disorder, which could have  
113 particularly broad implications for the outcome of cardiovascular morbidity and  
114 mortality.

115 Association of hepatic steatosis with CKD development and its impact on the  
116 reduction of the estimated glomerular filtration rate (eGFR) have been extensively  
117 investigated over the past decade <sup>4</sup>. The substantial evidence linked hepatic steatosis  
118 to the increased risk and severity of CKD, which may be a target for the prevention  
119 and treatment of the disease <sup>5</sup>. As a convenient scoring system for the presence of  
120 hepatic lipid deposits, the fatty liver index (FLI) is a surrogate steatosis biomarker  
121 developed in a cohort of patients from the general population <sup>6</sup>. Compared with other  
122 techniques for evaluating hepatic steatosis, FLI is simple to obtain as body mass index  
123 (BMI), waist circumference (WC), triglycerides (TG) and  $\gamma$ -glutamyltransferase  
124 ( $\gamma$ -GGT) are routine measurements in clinical practice. Previous studies have  
125 demonstrated that FLI could determine fatty liver disease, incident type 2 diabetes and

126 incident hypertension with considerable accuracy<sup>6-8</sup>. Moreover, FLI is associated with  
127 insulin resistance early atherosclerosis and risk of coronary heart disease, which could  
128 help physicians early detect subjects of greater cardiovascular risk and select patients  
129 for intensified lifestyle counseling<sup>9 10</sup>.

130 Clarified the association of FLI with albuminuria and prevalent CKD would  
131 probably shed light on the prevention and preemptive treatment of related diseases.  
132 Recently, a cross-sectional study was conducted to investigate the association between  
133 FLI and CKD by recruiting adults undergoing a health check-up<sup>11</sup>. However, by  
134 including only 731 subjects, the study did not evaluate the association between FLI  
135 and albuminuria, either. Therefore, we analyzed data from a community-based  
136 Chinese population to comprehensively look into the relationship of FLI with both  
137 increased urinary albumin excretion and CKD.

138  
139 **Subjects and methods**

140 **Study population and design**

141 We performed a cross-sectional study in a community in Guangzhou, China from  
142 June to November, 2011. The study population was from the REACTION study and  
143 details of this study have been published previously<sup>12-14</sup>. During the recruiting phase,  
144 a total of 10,104 residents aged 40 years or older were invited to participate by  
145 examination notices or home visits. In total, 9,916 subjects signed the consent form  
146 and agreed to participate in the survey, and the participation rate was 98.1%. The  
147 subjects who failed to provided information (BMI: n=206; WC: n=62; TG: n=23;

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2  
3  
4 148  $\gamma$ -GGT: n=38; or urinary albumin-to-creatinine ratio [ACR]: n=149) were excluded  
5  
6 149 from the analyses. Accordingly, a total of 9,438 eligible individuals were included in  
7  
8 150 the final data analyses. The study protocol was approved by the Institutional Review  
9  
10  
11 151 Board of the Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University and  
12  
13 152 was in accordance with the principle of the Helsinki Declaration II. Written informed  
14  
15 153 consent was obtained from each participant before data collection.  
16  
17

#### 18 154 **Clinical and biochemical measurements**

19  
20 155 We collected information on lifestyle factors, sociodemographic characteristics  
21  
22 156 and family history by using a standard questionnaire. Smoking or drinking habit was  
23  
24 157 classified as 'never', 'current' (smoking or drinking regularly in the past 6 months) or  
25  
26 158 'ever' (cessation of smoking or drinking more than 6 months)<sup>15</sup>. A short form of the  
27  
28 159 International Physical Activity Questionnaire (IPAQ) was used to estimate physical  
29  
30 160 activity at leisure time by adding questions on frequency and duration of moderate or  
31  
32 161 vigorous activities and walking<sup>16</sup>. Separate metabolic equivalent hours per week  
33  
34 162 (MET-h/week) were calculated for evaluation of total physical activity.  
35  
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37

38  
39 163 All participants completed anthropometrical measurements with the assistance of  
40  
41 164 trained staff by using standard protocols. Three times consecutively blood pressure  
42  
43 165 measurements by the same observer with a 5-minute interval were obtained by an  
44  
45 166 automated electronic device (OMRON, Omron Company, China). The average of  
46  
47 167 three measurements of blood pressure was used for analysis. Body height and body  
48  
49 168 weight were recorded to the nearest 0.1 cm and 0.1 kg while participants were  
50  
51 169 wearing light indoor clothing without shoes. BMI was calculated as weight in  
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170 kilograms divided by height in meters squared ( $\text{kg/m}^2$ ). Obesity was defined as BMI  
171 equal or greater than 28 and overweight was defined as BMI equal or greater than 24  
172 and less than 28<sup>17</sup>. WC was measured at the umbilical level with participant in  
173 standing position, at the end of gentle expiration.

174 Venous blood samples were collected for laboratory tests after an overnight  
175 fasting of at least 10 hours. Measurement of fasting plasma glucose (FPG), fasting  
176 serum insulin, TG, total cholesterol (TC), high-density lipoprotein cholesterol  
177 (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine,  $\gamma$ -GGT, aspartate  
178 aminotransferase (AST) and alanine aminotransferase (ALT) was done using an  
179 autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA).

180 As surrogate marker of hepatic steatosis, FLI was analyzed based on BMI, WC,  
181 TG, and  $\gamma$ -GGT, which has been validated against liver ultrasound in the general  
182 population and has been proven accurate in detecting fatty liver<sup>6 10</sup>. FLI is calculated  
183 as: 
$$\text{FLI} = \left( e^{0.953 * \log_e(\text{TG}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{GGT}) + 0.053 * \text{WC} - 15.745} \right) / \left( 1 + e^{0.953 * \log_e(\text{TG}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{GGT}) + 0.053 * \text{WC} - 15.745} \right) * 100$$
  
184 The  
185 abbreviated Modification of Diet in Renal Disease (MDRD) formula recalibrated for  
186 Chinese population was used to calculate estimated glomerular filtration rate (GFR)  
187 expressed in mL/min per  $1.73 \text{ m}^2$  using a formula of  $\text{eGFR} = 175 \times [\text{serum creatinine}$   
188  $\times 0.011]^{-1.234} \times [\text{age}]^{-0.179} \times [0.79 \text{ if female}]$ , where serum creatinine was expressed as  
189  $\mu\text{mol/L}$ <sup>18</sup>. Diabetes was diagnosed according to the 1999 World Health Organization  
190 diagnostic criteria<sup>19</sup>.

191 **Definition of increased urinary albumin excretion, chronic kidney disease and**

## 192 **non-alcoholic fatty liver disease (NAFLD)**

193 Definitions of abnormalities in albumin excretion were according to the latest  
194 guidelines of American Diabetes Association's Standards of Medical Care <sup>20</sup>. The first  
195 morning spot urine samples were collected for assessing the ACR. Urine albumin and  
196 creatinine were measured by chemiluminescence immunoassay (Siemens Immulite  
197 2000, United States) and the Jaffe's kinetic method (Biobase-Crystal, Jinan, China)  
198 on the automatic analyzer, respectively. ACR was calculated by dividing the urinary  
199 albumin concentrations by the urinary creatinine concentrations and expressed in  
200 mg/g. The primary and secondary outcome measures were increased urinary albumin  
201 excretion and chronic kidney disease (CKD), respectively. Increased urinary albumin  
202 excretion was defined according to the ACR ranges greater or equal than 30 mg/g.  
203 Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min per 1.73 m<sup>2</sup>  
204 or presence of albuminuria (ACR greater or equal than 30 mg/g). The optimal cutoff  
205 value of FLI for predicting NAFLD was 30 in Asian populations <sup>21</sup>. Therefore, we  
206 classified the study population in non-current drinking group into NAFLD group (FLI  
207  $\geq 30$ ) and non-NAFLD group (FLI  $< 30$ ).

## 209 **Statistical analysis**

210 Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary,  
211 NC, USA). Continuous variables were presented as means  $\pm$  standard deviation (SD)  
212 except for skewed variables, which were presented as medians (interquartile ranges).  
213 Categorical variables were expressed as numbers (proportions). FLI, FPG, TG, ALT,

214 AST,  $\gamma$ -GGT and MET-h/week were logarithmically transformed before analysis due  
215 to a non-normal distribution. FLI was presented as quartiles and linear regression  
216 analysis was used to test for trend across groups. Differences among groups were  
217 tested by one-way ANOVA and *post hoc* comparisons were performed by using  
218 Bonferroni correction. Comparisons between categorical variables were performed  
219 with the  $\chi^2$  test.

220 Pearson's correlations were performed to test the correlations between FLI and  
221 the risk factors for kidney disease. Variables significant at  $P < 0.20$  in Pearson's  
222 correlations were put into the multivariate stepwise linear regression models to  
223 identify factors that independently associated with FLI. We analyzed the impact of  
224 FLI on the prevalence of increased urinary albumin excretion and CKD. The  
225 unadjusted and multivariate-adjusted logistic regression analysis was used to assess  
226 the risk of prevalent increased urinary albumin excretion and CKD in relation to each  
227 quartile increase in FLI level. Variables considered as potential covariates and  
228 significant in the stepwise linear regression were put into multivariate-adjusted  
229 logistic regression analysis. Model 1 is unadjusted. Model 2 is adjusted for age. Model  
230 3 is adjusted for age, sex, current smoking status, current drinking status, physical  
231 activity, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL-C,  
232 fasting insulin, ALT and AST. Model 4 is adjusted for age, sex, BMI, WC, current  
233 smoking status, current drinking status, physical activity, systolic blood pressure  
234 (SBP), diastolic blood pressure (DBP), TG, LDL-C, fasting insulin, ALT, AST and  
235  $\gamma$ -GGT. Odds ratios (OR) and the corresponding 95% confidence intervals (95% CI)

were calculated. Relationship of FLI level with albuminuria and CKD were also explored in subgroups stratified by gender (men/women), age ( $\geq 60$ / $< 60$  years), degree of obesity (normal/overweight/obesity), current smoking (yes/no), current drinking (yes/no), hypertension (yes/no) and diabetes (yes/no). Tests for interaction were performed with including simultaneously each strata factor, the quartiles of FLI level and the respective interaction terms (strata factor multiplied by quartiles of FLI level) in the models.

All statistical tests were two-sided, and a P value  $< 0.05$  was considered statistically significant.

## Results

### Clinical characteristics of the study population

Among the 9,436 enrolled individuals, the mean age was  $55.9 \pm 8.0$  years. The median FLI was 19.1 with interquartile range 8.6 to 37.4. There were 620 (6.6%) subjects categorized as increased urinary albumin excretion and 753 (8.0%) subjects categorized as CKD, respectively. Table 1 shows the clinical and biochemical characteristics of the participants according to FLI quartiles. Participants with higher FLI level had elevated age, BMI, WC, SBP, DBP, TG, TC, LDL-C, FPG, fasting insulin, ALT, AST,  $\gamma$  - GGT and higher proportions of current smokers and current drinkers (all P for trend  $< 0.0001$ ). Those with higher FLI level also associated with decreased HDL-C and eGFR (all P for trend  $< 0.0001$ ).

### Associations between FLI and metabolic risk factors

Analysis of Pearson’s correlation showed that age, sex, BMI, WC, SBP, DBP, TG, TC, HDL-C, LDL-C, FPG, fasting insulin, ALT, AST,  $\gamma$ -GGT and eGFR were significantly correlated with FLI level. Further multivariate stepwise linear regression showed that age, sex, BMI, WC, SBP, DBP, TG, LDL-C, fasting insulin, ALT, AST and  $\gamma$ -GGT were independent determinants for FLI level (Table 2).

**Associations of FLI with increased urinary albumin excretion and CKD**

As shown in Figure.1A, from the lowest quartile to the highest quartile of FLI level, the prevalence of increased urinary albumin excretion was 3.64%, 4.83%, 6.23% and 11.57%, respectively (P for trend < 0.0001). Strikingly, the prevalence of CKD also tended to increase with the elevated FLI quartile (Figure.1B, P for trend < 0.0001). As shown in Table 3, compared with participants in quartile 1 of FLI, univariate logistic regression analysis showed that participants in quartile 2, quartile 3 and quartile 4, respectively, have a significant correlation with increased odds of increased urinary albumin excretion and CKD (all P for trend < 0.0001). In multivariate logistic regression analyses (Model 3), the ORs of increased urinary albumin excretion for increasing FLI quartiles were 1.00 (reference), 0.96 (95% CI 0.66 - 1.39), 1.17 (95% CI 0.77 - 1.77) and 2.30 (95% CI 1.36 - 3.90). Similarly, the ORs of CKD for increasing FLI quartiles in Model 3 were 1.00 (reference), 1.00 (95% CI 0.71 - 1.40), 1.03 (95% CI 0.70 - 1.51) and 1.93 (95% CI 1.18 - 3.15), respectively (Table 3). The prevalence of increased urinary albumin excretion was 51.6% and 29.6% in FLI established NAFLD and non-NAFLD group (P < 0.0001). Similar trends were detected in the prevalence of CKD (NAFLD group: 49.9%; non-NAFLD

group: 31.5%,  $P < 0.0001$ ). Compared with participants in the non-NAFLD group, those in NAFLD group had higher prevalence of increased urinary albumin excretion (OR 1.58, 95 % CI 1.18 - 2.13) and CKD (OR 1.39, 95 % CI 1.05 - 1.82) in multivariate logistic regression analyses.

#### **Subgroups analysis of FLI with increased urinary albumin excretion and CKD**

As shown in Figure. 2 & 3, the associations of FLI level with increased urinary albumin excretion and CKD were not consistently the same in subgroups analyses. Significant relationship of FLI level with both increased urinary albumin excretion and CKD were detected in women, younger subjects (age less than 60 years), overweight subjects, non-current smokers, non-current drinkers and in those with hypertension or with diabetes (all  $P < 0.05$ ). In the subgroups analysis, no statistically significance of interaction term between quartiles of FLI and each strata factor was detected.

#### **Discussion**

We evaluated the association between hepatic steatosis and kidney disease in a large population of middle-age Chinese subjects from the REACTION study. Presence of fatty liver assessed by FLI was associated with increased urinary albumin excretion and reduction of the eGFR in the present study. The association was independent of potential confounding risk factors. To our current knowledge, this is the largest population-based study to explore the association of FLI with both albuminuria and CKD in Asian population. Early intervention is of great importance

for albuminuria and CKD, the present findings may just give insights into lipid metabolism for prevention and early detection of the diseases.

Prevalence of obesity was 7.9% (8.4% in males and 7.6% in females) in southern China, which has increased dramatically over the past several decades<sup>22</sup>. The best method for an accurate assessment and diagnosis of hepatic steatosis is histologic analysis of biopsies<sup>23</sup>. However, it is uneconomical to conduct liver biopsies especially by the fact of our large sample population. Hepatic ultrasonic examination is widely used in clinical practice and epidemiological studies in detecting fatty infiltration of the liver<sup>24 25</sup>. However, the noninvasive technique is not sensitive enough to detect mild steatosis and does not allow precise quantification of severity of steatosis in hepatic tissue<sup>26</sup>. As another surrogate marker of histological fatty liver, FLI is defined as the accumulation of excessive liver fat<sup>27</sup>. Based on the former researches, FLI has been proven accurate in detecting fatty liver against liver ultrasound and demonstrating the presence of hepatic fat against magnetic resonance spectroscopy<sup>6 9 10 21</sup>. The superiority of this non-invasive assessment techniques is that a higher score will indicate a higher degree of steatosis in hepatic tissue. However, optimal cut-off point of the FLI for evaluating liver fatty infiltration should be considered as it varied according to the study population<sup>21 28</sup>. Originally, FLI>60 was suggested to rule in NAFLD in Caucasian subjects. However, the optimal cut-off value of FLI for predicting NAFLD was different in Asian populations. In one recent study, Huang et al.<sup>21</sup> found that FLI could accurately identify NAFLD and the optimal cut-off point was 30 in middle-aged and elderly Chinese. FLI could also

324 accurately identify ultrasonography fatty liver in a large scale population in Taiwan  
325 but with different optimal cut-off values, while an  $FLI > 35$  for males and  $> 20$  for  
326 females rule in NAFLD in their study<sup>28</sup>. Through the results of our research in  
327 Chinese subjects, further studies are therefore needed to externally discuss the optimal  
328 cut-off point of the FLI for predicting hepatic steatosis.

329 Detection and prevention of kidney disease progression and urinary albumin  
330 excretion is difficult to process in the early stage. Dyslipidemia is increasingly  
331 recognized as important pathogenic mechanism in deterioration of renal function.  
332 Recently, we conducted a clinical investigation to assess the associations of routine  
333 lipid measures with kidney disease in the same cohort. In the study, discordant  
334 associations of lipid parameters with renal insufficiency was detected while TG to  
335 HDL-C ratio is a better marker for evaluating increased urinary albumin excretion and  
336 CKD<sup>29</sup>. As one of the phenotype of dyslipidemia, the pathogenesis of hepatic  
337 steatosis is closely related to kidney disease with regard to insulin resistance and  
338 chronic inflammation<sup>30</sup>. Hepatokines, which are proteins secreted by hepatocytes,  
339 have been found to link to the induction of metabolic phenotypes through inter-organ  
340 communication based on recent studies<sup>31</sup>. Because of the high prevalence and burden  
341 of the fatty liver disease, it is important to identify which patients are most likely to be  
342 exposed to early stage renal injury<sup>32</sup>. Consequently, we closely monitor the  
343 association of the hepatic steatosis predict by FLI with prevalent increased urinary  
344 albumin excretion and CKD.

345 Consistent with our findings, a previous study reported that hepatic steatosis

346 evaluated by FLI might contribute to CKD development <sup>11</sup>. Elevated albuminuria is  
347 well known to be associated with increased risk for early diabetes renal damage,  
348 however, the identification and classification of kidney disease was assessed only by  
349 eGFR in that study. Moreover, 731 adults that underwent routine health evaluations  
350 were included in that study and the small sample size cannot better represent the  
351 whole population. By totally including 9,438 subjects and adopting both albuminuria  
352 and eGFR for renal damage assessment, data in our study demonstrated that the FLI is  
353 associated with kidney disease, which might be an efficient screening indicator for the  
354 early prevention of related diseases in Chinese subjects. Recently, an interesting study  
355 by Giorda C et al. <sup>33</sup> reported that NAFLD is a dynamic condition in type 2 diabetes  
356 subjects and about 5% Italian diabetic patients entering or leaving FLI assessed  
357 NAFLD status every year. They found that male sex and established organ damage,  
358 especially kidney function, were independent risk predictors for the dynamic NAFLD  
359 condition in a longitudinal 3-year analysis. As the similarity in traditional risk factors  
360 for both NAFLD and CKD, relationship between the prevalence of earlier stages of  
361 kidney damage and the incidence of NAFLD is complex. Longitudinal observation of  
362 our cohort are needed to be carried out to determine whether such dynamic condition  
363 existed in the Chinese, especially in those with type 2 diabetes.

364 Alcohol consumption can profoundly disturb the lipid metabolism which have  
365 prominent effects on the hepatic tissue steatosis and insulin sensitivity <sup>34</sup>. However,  
366 potential health effects regarding alcohol consumption in this field is also worth  
367 attaching attention. A meta-analysis of intervention studies by Schrieke et al <sup>35</sup>.

showed that moderate alcohol intake could improve insulin sensitivity by decreasing fasting insulin level in women. Recently, a prospective cohort study found that alcohol consumption was consistently inversely associated with urinary albumin excretion and the risk of developing CKD <sup>36</sup>. Therefore, advice concerning alcohol consumption to subjects with low-grade hepatic tissue steatosis should consider the full range of benefits and risks, especially among those who drink moderately.

Some limitations of the study must be noted. Firstly, owing to the observational design of the current study, we should cautiously interpret the present findings as no causal inference can be drawn. Further prospective studies are therefore needed to determine the precise relationship between FLI and risk of renal diseases. Secondly, by including only Chinese subjects, the results of the present study might not be representative of other ethnic groups, especially for those in the developed or undeveloped countries. To some extent, however, the present study of Chinese population was still a convenience sample and selection bias is inevitable. Thirdly, when evaluating the findings of the present study, the results should be interpreted cautiously due to possible bias from using the indirect indicator FLI to assess fatty liver disease. Moreover, the internal accuracy of FLI for evaluation hepatic steatosis should also be validated by using other techniques, before it can be employed for these purposes. Fourthly, we observed that FLI seem to play a different efficiency for kidney disease assessment in different stratifications. A significant association of FLI with increased urinary albumin excretion and CKD only detected in subjects without current alcohol consumption. Average daily alcohol intake influences the FLI and

390 missing such data in the present study doesn't permit comparisons between and within  
391 alcoholic and nonalcoholic fatty liver disease groups. To better discriminate alcoholic  
392 fatty liver disease and non-alcoholic fatty liver disease, further studies need to clearly  
393 described the precise exposure of alcohol use by collecting histories of alcohol intake  
394 in a quantitative manner. Fifthly, viral hepatitis infection is one of the most serious  
395 infectious diseases worldwide, which can be associated with both liver and kidney  
396 disease. Recent survey data showed that the hepatitis B surface antigen and  
397 anti-hepatitis C virus-positive rates were already 6.1% and 3.0% in China.  
398 Epidemiology of viral hepatitis infection by hepatitis B virus (HBV) and hepatitis C  
399 virus (HCV) serological testing, therefore, should be also be evaluate to strength the  
400 findings of the present study <sup>37</sup>. Sixthly, although a spectrum of covariates was  
401 included in the adjustment, other potential mediators such as daily energy and protein  
402 intake and medicine that influence the renin-angiotensin-system of the subjects,  
403 should also be considered in the present study.

404 In conclusion, by including a large population based cohort, the present study  
405 provides evidence that increased FLI is independently associated with prevalence of  
406 albuminuria and CKD. Further prospective studies are necessary to verify our  
407 findings in external populations.

410

411 **Figure legends**

412

413 **Figure. 1** Prevalence of increased urinary albumin excretion and CKD in different quartiles of  
414 FLI levels. (A) Increased urinary albumin excretion. (B) CKD.

415

416 **Figure. 2** Risk of prevalent increased urinary albumin excretion with each quartile increase of  
417 FLI levels in different subgroups.

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419 **Figure. 3** Risk of prevalent CKD with each quartile increase of FLI levels in different  
420 subgroups.

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Table 1. Characteristics of study population by FLI quartiles					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
n (%)	2360 (25.01)	2359 (24.99)	2359 (24.99)	2360 (25.01)	
Fatty liver index	5.00 (3.27 – 6.74)	13.23 (10.76 – 15.99)	26.96 (22.74 – 31.75)	54.71 (45.40 – 68.10)	
Urinary albumin to creatinine ratio (mg/g)	7.65 (5.59 – 11.12)	8.01 (5.64 – 11.71)	8.06 (5.73 – 11.83)*	8.93 (5.96 – 15.01)*#&	< 0.0001
Age (years)	54.3 ± 7.8	55.8 ± 7.9*	56.5 ± 7.9*#	56.9 ± 8.3*#	< 0.0001
Male [n (%)]	427 (18.09)	593 (25.17)	701 (29.72)	975 (41.31)	< 0.0001
BMI (kg/m <sup>2</sup> )	20.6 ± 2.0	22.9 ± 2.0*&	24.4 ± 2.1*#	26.8 ± 3.5*#&	< 0.0001
WC (cm)	72.0 ± 5.8	79.3 ± 5.4*&	84.1 ± 5.5*#	91.3 ± 8.5*#&	< 0.0001
SBP (mmHg)	118.6 ± 14.7	124.5 ± 15.9*&	128.4 ± 15.8*#	132.5 ± 16.1*#&	< 0.0001
DBP (mmHg)	71.2 ± 9.1	74.2 ± 9.3*&	76.5 ± 9.4*#	79.3 ± 9.8*#&	< 0.0001
Current smoking [n (%)]	169 (7.3)	202 (8.7)	227 (9.8)	335 (14.4)	< 0.0001
Current drinking [n (%)]	57 (2.5)	70 (3.0)	68 (2.9)	117 (5.1)	< 0.0001
TG (mmol/L)	0.85 (0.69 – 1.07)	1.12 (0.90 – 1.43)*&	1.49 (1.13 – 1.94)*#	2.10 (1.56 – 3.01)*#&	< 0.0001
TC (mmol/L)	4.79 ± 1.24	5.16 ± 1.22*&	5.35 ± 1.13*#	5.54 ± 1.17*#&	< 0.0001
HDL-C (mmol/L)	1.45 ± 0.41	1.37 ± 0.35*&	1.29 ± 0.31*#	1.19 ± 0.28*#&	< 0.0001

LDL-C (mmol/L)	2.82 ± 0.90	3.19 ± 0.94 <sup>*&amp;</sup>	3.31 ± 0.91 <sup>*#</sup>	3.28 ± 0.95 <sup>*#</sup>	< 0.0001
FPG (mmol/L)	5.23 (4.89 – 5.61)	5.33 (4.95 – 5.80) <sup>*&amp;</sup>	5.47 (5.05 – 5.96) <sup>*#</sup>	5.73 (5.23 – 6.42) <sup>*#&amp;</sup>	< 0.0001
Fasting insulin (μIU/ml)	5.10 (3.90 – 6.50)	6.50 (5.00 – 8.40) <sup>*&amp;</sup>	7.90 (6.10 – 10.30) <sup>*#</sup>	10.50 (7.80 – 13.70) <sup>*#&amp;</sup>	< 0.0001
ALT (U/L)	10.0 (8.0 – 14.0)	12.0 (9.0 – 16.0) <sup>*&amp;</sup>	13.0 (10.0 – 17.0) <sup>*#</sup>	17.0 (12.0 – 24.0) <sup>*#&amp;</sup>	< 0.0001
AST (U/L)	17.0 (14.0 – 20.0)	18.0 (15.0 – 21.0) <sup>*&amp;</sup>	18.0 (15.0 – 22.0) <sup>*#</sup>	20.0 (17.0 – 25.0) <sup>*#&amp;</sup>	< 0.0001
γ-GGT (U/L)	14.0 (11.0 – 17.0)	18.0 (14.0 – 23.0) <sup>*&amp;</sup>	22.0 (17.0 – 29.0) <sup>*#</sup>	31.0 (23.0 – 47.0) <sup>*#&amp;</sup>	< 0.0001
Serum creatinine (μmol/L)	65.3 ± 15.5	68.8 ± 16.0 <sup>*&amp;</sup>	70.5 ± 16.0 <sup>*#</sup>	74.9 ± 17.2 <sup>*#&amp;</sup>	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	108.0 ± 25.4	102.5 ± 23.7 <sup>*&amp;</sup>	99.9 ± 19.6 <sup>*#</sup>	95.5 ± 19.5 <sup>*#&amp;</sup>	< 0.0001
Physical activity (MET-h/week)	24.0 (10.5 – 49.0)	24.0 (10.5 – 45.0)	23.0 (10.5 – 42.0)	21.0 (10.5 – 42.0) <sup>*</sup>	0.006
<p>1. Data were means ± SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.</p> <p>2. P for trend was calculated for the linear regression analysis tests across the groups. P values were for the ANOVA or <math>\chi^2</math> analyses across the groups.</p> <p>3. *P &lt; 0.05 compared with Quartile 1 of fatty liver index; #P &lt; 0.05 compared with Quartile 2 of fatty liver index; &amp;P &lt; 0.05 compared with Quartile 3 of fatty liver index.</p> <p>4. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyltransferase; eGFR, estimated glomerular filtration rate.</p>					

**Table 2.** Pearson’s correlation and stepwise regression analysis of determinants of FLI

	r	P value	Standardized $\beta$	P value
Age (years)	0.12	< 0.0001	0.01	0.010
Sex (men=1, women=2)	-0.19	< 0.0001	-0.04	< 0.0001
BMI (kg/m <sup>2</sup> )	0.71	< 0.0001	0.30	< 0.0001
WC (cm)	0.78	< 0.0001	0.42	< 0.0001
Physical activity (MET-h/week)	-0.02	0.060	-	-
SBP (mmHg)	0.32	< 0.0001	0.01	0.006
DBP (mmHg)	0.32	< 0.0001	0.01	0.047
TG (mmol/L)	0.68	< 0.0001	0.42	< 0.0001
HDL-C (mmol/L)	-0.26	< 0.0001	-	-
LDL-C (mmol/L)	0.21	< 0.0001	0.06	< 0.0001
FPG (mmol/L)	0.22	< 0.0001	-	-
Fasting insulin ( $\mu$ IU/ml)	0.40	< 0.0001	0.01	0.0002
ALT (U/L)	0.20	< 0.0001	0.05	< 0.0001
AST (U/L)	0.15	< 0.0001	-0.03	< 0.0001
$\gamma$ -GGT (U/L)	0.35	< 0.0001	0.16	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	-0.19	< 0.0001	-	-

r, correlation coefficient;  $\beta$ , regression coefficient.

**Table 3.** The risk of prevalent albuminuria and CKD according to quartiles of FLI

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Increased urinary albumin excretion	Model 1	1	1.34 (1.01 – 1.79)	1.76 (1.34 – 2.31)	3.46 (2.70 – 4.44)	< 0.0001
	Model 2	1	1.29 (0.97 – 1.72)	1.66 (1.27 – 2.19)	3.25 (2.53 – 4.17)	< 0.0001
	Model 3	1	0.94 (0.66 – 1.33)	1.13 (0.81 – 1.59)	2.22 (1.60 – 3.07)	< 0.0001
	Model 4	1	0.96 (0.66 – 1.39)	1.17 (0.77 – 1.77)	2.30 (1.36 – 3.90)	0.001
CKD	Model 1	1	1.47 (1.13 – 1.90)	1.79 (1.39 – 2.30)	3.49 (2.77 – 4.39)	< 0.0001
	Model 2	1	1.39 (1.07 – 1.80)	1.65 (1.28 – 2.12)	3.16 (2.51 – 3.99)	< 0.0001
	Model 3	1	0.99 (0.73 – 1.36)	1.03 (0.75 – 1.40)	1.95 (1.44 – 2.64)	< 0.0001
	Model 4	1	1.00 (0.71 – 1.40)	1.03 (0.70 – 1.51)	1.93 (1.18 – 3.15)	0.012

Data are odds ratios (95% confidence interval). Participants without increased urinary albumin excretion or CKD are defined as 0 and with increased urinary albumin excretion or CKD as 1.

Model 1 is unadjusted.

Model 2 is adjusted for age.

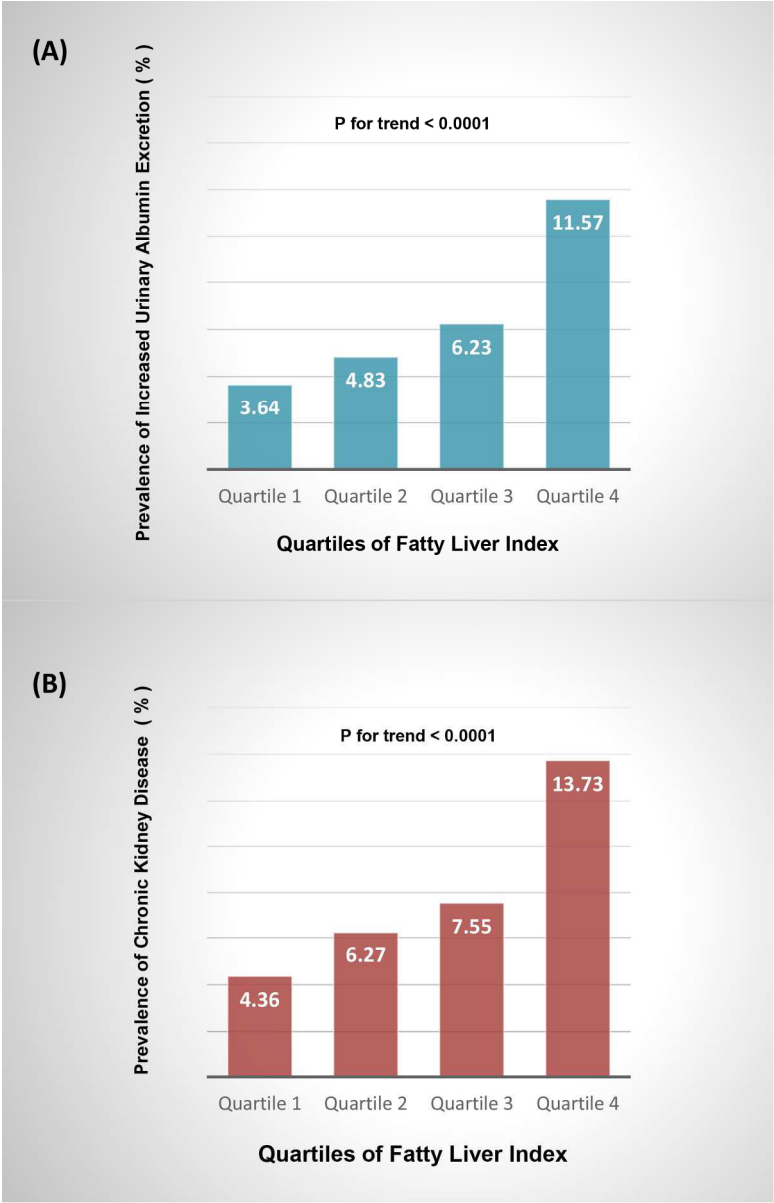
Model 3 is adjusted for age, sex, current smoking status, current drinking status, physical activity, SBP, DBP, LDL-C, fasting insulin, ALT and AST.

Model 4 is adjusted for age, sex, BMI, WC, current smoking status, current drinking status, physical activity, SBP, DBP, TG, LDL-C, fasting insulin, ALT,

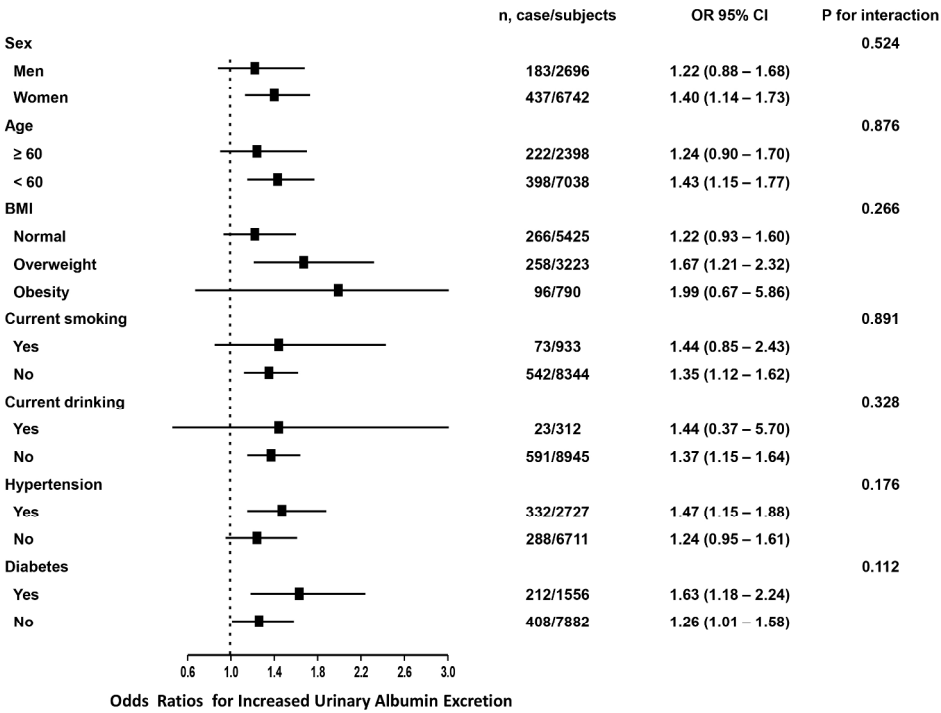
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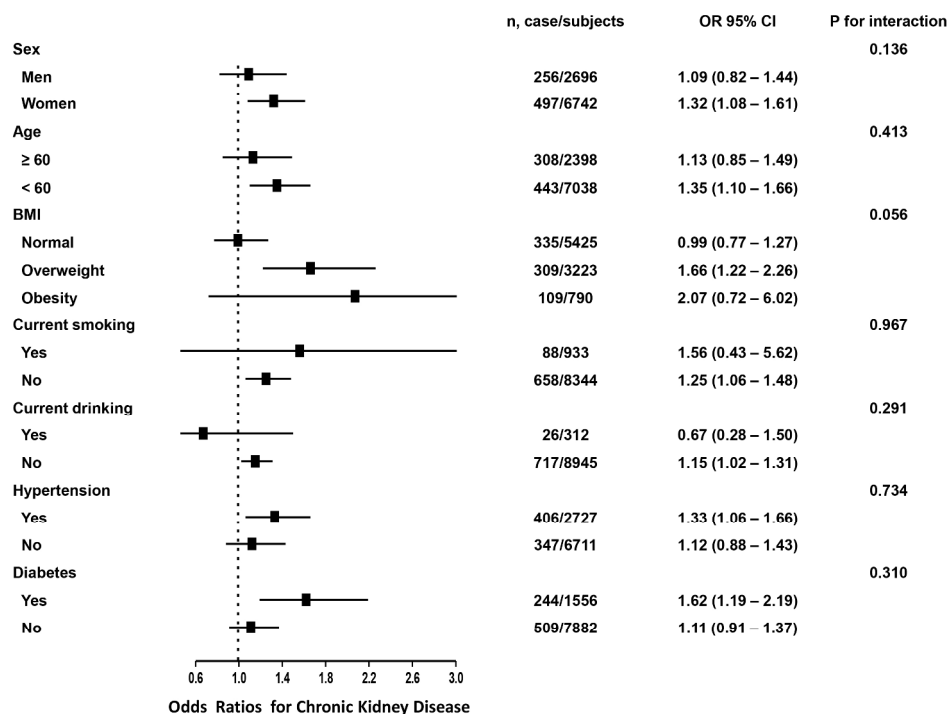
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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	L 1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	L 67-91
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	L 105-137
Objectives	3	State specific objectives, including any prespecified hypotheses	L 130-137
Methods			
Study design	4	Present key elements of study design early in the paper	L 141-146
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	L 141-179
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	L 141-153
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	L 155-207
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	L 193-207
Bias	9	Describe any efforts to address potential sources of bias	L 227-242
Study size	10	Explain how the study size was arrived at	L 143-146
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	L 210-219
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	L 210-242
		(b) Describe any methods used to examine subgroups and interactions	L 236-239
		(c) Explain how missing data were addressed	N.A.
		(d) If applicable, describe analytical methods taking account of sampling strategy	N.A.
		(e) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	L 248-256
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	L 248-262
		(b) Indicate number of participants with missing data for each variable of	L 248-

		interest	292
Outcome data	15*	Report numbers of outcome events or summary measures	L 264-283
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	L 264-283
		(b) Report category boundaries when continuous variables were categorized	L 210-219
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	L 285-292
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	L 295-303
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	L 374-403
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	L 329-373
Generalisability	21	Discuss the generalisability (external validity) of the study results	L 377-381
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	L 47-59

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Fatty liver index is associated with albuminuria and chronic kidney disease: a population-based study

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Keywords:	Fatty liver index, Hepatic steatosis, ncreased urinary albumin excretion, Chronic kidney disease

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Manuscripts

**Fatty liver index is associated with albuminuria and chronic kidney disease: a population-based study**

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**#Kan Sun and Diaozhu Lin contributed equally to this work.**

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## **Statement of authorship**

All authors believe that the manuscript represents valid work and have reviewed and approved the final version. The work has not been published previously, and not under consideration for publication elsewhere, in part or in whole.

## **The author contribution lists**

Conceived and designed the experiments: Y. L. and K. S.

Performed the experiments: F. L., Y. Q., W. F., C. C., K. S. and D. L.

Analyzed the data: K. S. and M. R.

Wrote the manuscript: K.S. and D. L.

## **Data Sharing Statement**

The work described was original research that has not been published previously, and not under consideration for publication elsewhere, in part or in whole. All authors believe that the manuscript represents valid work and have reviewed and approved the final version. Main document data and additional unpublished data from the study are available by sending Email to lizyhenu@163.com with proper purposes.

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45

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58 had no role in study design, data collection and analysis, decision to publish, or  
59 preparation of the manuscript.

60

61 **Conflict of interests**

62 The authors have declared that no competing interests exist.

63

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65

66 **ABSTRACT**

67 **Objectives:** The effects of lipid metabolism disorder on the renal damage have drawn  
68 much attention. By using the fatty liver index (FLI) as a validated indicator of hepatic  
69 steatosis, this study aims at provide insight about the possible links between fatty liver  
70 and development of chronic kidney disease (CKD).

71 **Setting:** hospital.

72 **Participants:** We performed a population-based study in 9,436 subjects aged 40 years  
73 or older.

74 **Primary and secondary outcome measures:** FLI is calculated by using an algorithm  
75 based on body mass index (BMI), waist circumference (WC), triglycerides (TG) and  
76  $\gamma$ -glutamyltransferase ( $\gamma$ -GGT). Increased urinary albumin excretion was defined  
77 according to the urinary albumin-to-creatinine ratio ranges greater or equal than 30  
78 mg/g. CKD was defined as estimated glomerular filtration rate (eGFR) less than 60  
79 mL/min per 1.73 m<sup>2</sup> or presence of albuminuria.

80 **Results:** There were 620 (6.6%) subjects categorized as increased urinary albumin  
81 excretion and 753 (8.0%) subjects categorized as CKD. Participants with higher FLI  
82 had increased age, blood pressure, low-density lipoprotein cholesterol, fasting plasma  
83 glucose, fasting insulin and decreased eGFR level. Prevalence of increased urinary  
84 albumin excretion and CKD tended to increase with the elevated FLI quartiles. In  
85 logistic regression analysis, compared with subjects in the lowest quartile of FLI, the  
86 adjusted odds ratios (ORs) in the highest quartile was 2.30 [95% confidence interval

(CI), 1.36 - 3.90] for increased urinary albumin excretion and 1.93 (95% CI, 1.18 - 3.15) for CKD.

**Conclusion:** Hepatic steatosis evaluating by FLI is independently associated with increased urinary albumin excretion and prevalence of CKD in middle-aged and elderly Chinese.

**Keywords:** Fatty liver index; Hepatic steatosis; Increased urinary albumin excretion; Chronic kidney disease

**Strengths and Limitations**

1. The study was performed in a large population-based cohort in 9,436 Chinese subjects.
2. Findings of the study may be applied to the majority of patients in general practice with suspected hepatic steatosis.
3. Results should be interpreted cautiously due to the observational design of the current study.

## 104 Introduction

105 Chronic kidney disease (CKD) has become one of the leading public health  
106 problem world-wide <sup>1</sup>. Recent national survey conducted between 2007 and 2010  
107 reports that the prevalence of CKD was 10.8%, representing an estimated 119.5  
108 million patients in China are with chronic kidney damage <sup>2</sup>. In addition to CKD, an  
109 increasing number of studies have provided substantial evidence of albuminuria as a  
110 risk factor for future cardiovascular events <sup>3</sup>. Both renal and cardiovascular diseases  
111 sharing similar traditional risk factors, such as lipid metabolism disorder, could have  
112 particularly broad implications for the outcome of cardiovascular morbidity and  
113 mortality.

114 Association of hepatic steatosis with CKD development and its impact on the  
115 reduction of the estimated glomerular filtration rate (eGFR) have been extensively  
116 investigated over the past decade <sup>4</sup>. The substantial evidence linked hepatic steatosis  
117 to the increased risk and severity of CKD, which may be a target for the prevention  
118 and treatment of the disease <sup>5</sup>. As a convenient scoring system for the presence of  
119 hepatic lipid deposits, the fatty liver index (FLI) is a surrogate steatosis biomarker  
120 developed in a cohort of patients from the general population <sup>6</sup>. Compared with other  
121 techniques for evaluating hepatic steatosis, FLI is simple to obtain as body mass index  
122 (BMI), waist circumference (WC), triglycerides (TG) and  $\gamma$ -glutamyltransferase  
123 ( $\gamma$ -GGT) are routine measurements in clinical practice. Previous studies have  
124 demonstrated that FLI could determine fatty liver disease, incident type 2 diabetes and  
125 incident hypertension with considerable accuracy <sup>6-8</sup>. Moreover, FLI is associated with

126 insulin resistance early atherosclerosis and risk of coronary heart disease, which could  
127 help physicians early detect subjects of greater cardiovascular risk and select patients  
128 for intensified lifestyle counseling<sup>9 10</sup>.

129 Clarifying the association of FLI with albuminuria and prevalent CKD would  
130 probably shed light on the prevention and preemptive treatment of related diseases.  
131 Recently, a cross-sectional study was conducted to investigate the association between  
132 FLI and CKD by recruiting adults undergoing a health check-up<sup>11</sup>. However, by  
133 including only 731 subjects, the study did not evaluate the association between FLI  
134 and albuminuria, either. Therefore, we analyzed data from a community-based  
135 Chinese population to comprehensively look into the relationship of FLI with both  
136 increased urinary albumin excretion and CKD.

137

138 **Subjects and methods**

139 **Study population and design**

140 We performed a cross-sectional study in a community in Guangzhou, China from  
141 June to November, 2011. The study population was from the REACTION study and  
142 details of this study have been published previously<sup>12-14</sup>. During the recruiting phase,  
143 a total of 10,104 residents aged 40 years or older were invited to participate by  
144 examination notices or home visits. In total, 9,916 subjects signed the consent form  
145 and agreed to participate in the survey. The participation rate was 98.1%. The subjects  
146 who failed to provide information (BMI: n=206; WC: n=62; TG: n=23;  $\gamma$ -GGT: n=38;  
147 or urinary albumin-to-creatinine ratio [ACR]: n=149) were excluded from the

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4 148 analyses. Accordingly, a total of 9,438 eligible individuals were included in the final  
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6 149 data analyses. The study protocol was approved by the Institutional Review Board of  
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8 150 the Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University and was in  
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11 151 accordance with the principle of the Helsinki Declaration II. Written informed consent  
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13 152 was obtained from each participant before data collection.  
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### 15 153 **Clinical and biochemical measurements**

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18 154 We collected information on lifestyle factors, sociodemographic characteristics  
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21 155 and family history by using a standard questionnaire. Smoking or drinking habit was  
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23 156 classified as 'never', 'current' (smoking or drinking regularly in the past 6 months) or  
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25 157 'ever' (cessation of smoking or drinking more than 6 months)<sup>15</sup>. A short form of the  
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28 158 International Physical Activity Questionnaire (IPAQ) was used to estimate physical  
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31 159 activity at leisure time by adding questions on frequency and duration of moderate or  
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33 160 vigorous activities and walking<sup>16</sup>. Separate metabolic equivalent hours per week  
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35 161 (MET-h/week) were calculated for evaluation of total physical activity.  
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38 162 All participants completed anthropometrical measurements with the assistance  
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41 163 of trained staff by using standard protocols. Three times consecutively blood pressure  
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43 164 measurements by the same observer in a 5-minute interval were obtained by an  
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45 165 automated electronic device (OMRON, Omron Company, China). The average of  
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48 166 three measurements of blood pressure was used for analysis. Body height and body  
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51 167 weight were recorded to the nearest 0.1 cm and 0.1 kg while participants were  
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53 168 wearing light indoor clothing without shoes. BMI was calculated as weight in  
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55 169 kilograms divided by height in meters squared ( $\text{kg/m}^2$ ). Obesity was defined as BMI  
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170 equal or greater than 28 and overweight was defined as BMI equal or greater than 24  
171 and less than 28<sup>17</sup>. WC was measured at the umbilical level with participant in  
172 standing position, at the end of gentle expiration.

173 Venous blood samples were collected for laboratory tests after an overnight  
174 fasting of at least 10 hours. Measurement of fasting plasma glucose (FPG), fasting  
175 serum insulin, TG, total cholesterol (TC), high-density lipoprotein cholesterol  
176 (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine,  $\gamma$ -GGT, aspartate  
177 aminotransferase (AST) and alanine aminotransferase (ALT) was done using an  
178 autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA).

179 As surrogate marker of hepatic steatosis, FLI was analyzed based on BMI, WC,  
180 TG, and  $\gamma$ -GGT, which has been validated against liver ultrasound in the general  
181 population and has been proven accurate in detecting fatty liver<sup>6 10</sup>. FLI is calculated  
182 as:  $FLI = (e^{0.953 * \log_e(TG) + 0.139 * BMI + 0.718 * \log_e(GGT) + 0.053 * WC - 15.745}) / (1$   
183  $+ e^{0.953 * \log_e(TG) + 0.139 * BMI + 0.718 * \log_e(GGT) + 0.053 * WC - 15.745}) * 100$ . The  
184 abbreviated Modification of Diet in Renal Disease (MDRD) formula recalibrated for  
185 Chinese population was used to calculate estimated glomerular filtration rate (GFR)  
186 expressed in mL/min per 1.73 m<sup>2</sup> using a formula of  $eGFR = 175 \times [\text{serum creatinine}$   
187  $\times 0.011]^{-1.234} \times [\text{age}]^{-0.179} \times [0.79 \text{ if female}]$ , where serum creatinine was expressed as  
188  $\mu\text{mol/L}$ <sup>18</sup>. Diabetes was diagnosed according to the 1999 World Health Organization  
189 diagnostic criteria<sup>19</sup>.

190 **Definition of increased urinary albumin excretion, chronic kidney disease and**  
191 **non-alcoholic fatty liver disease (NAFLD)**

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4 192 Definitions of abnormalities in albumin excretion were according to the latest  
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6 193 guidelines of American Diabetes Association's Standards of Medical Care<sup>20</sup>. The first  
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8 194 morning spot urine samples were collected for assessing the ACR. Urine albumin and  
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11 195 creatinine were measured by chemiluminescence immunoassay (Siemens Immulite  
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13 196 2000, United States) and the Jaffe's kinetic method (Biobase-Crystal, Jinan, China)  
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16 197 on the automatic analyzer, respectively. ACR was calculated by dividing the urinary  
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18 198 albumin concentrations by the urinary creatinine concentrations and expressed in  
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20 199 mg/g. The primary and secondary outcome measures were increased urinary albumin  
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23 200 excretion and chronic kidney disease (CKD), respectively. Increased urinary albumin  
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26 201 excretion was defined according to the ACR ranges greater or equal than 30 mg/g.  
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28 202 Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min per 1.73 m<sup>2</sup>  
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30 203 or presence of albuminuria (ACR greater or equal than 30 mg/g). The optimal cutoff  
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33 204 value of FLI for predicting NAFLD was 30 in Asian populations<sup>21</sup>. Therefore, we  
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35 205 classified the study population in non-current drinking group into NAFLD group (FLI  
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38 206  $\geq 30$ ) and non-NAFLD group (FLI < 30).

## 207 208 **Statistical analysis**

209 Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary,  
210 NC, USA). Continuous variables were presented as means  $\pm$  standard deviation (SD)  
211 except for skewed variables, which were presented as medians (interquartile ranges).  
212 Categorical variables were expressed as numbers (proportions). FLI, FPG, TG, ALT,  
213 AST,  $\gamma$ -GGT and MET-h/week were logarithmically transformed before analysis due

214 to a non-normal distribution. FLI was presented as quartiles and linear regression  
215 analysis was used to test for trend across groups. Differences among groups were  
216 tested by one-way ANOVA and *post hoc* comparisons were performed by using  
217 Bonferroni correction. Comparisons between categorical variables were performed  
218 with the  $\chi^2$  test.

219 Pearson's correlations were performed to test the correlations between FLI and  
220 the risk factors for kidney disease. Variables significant at  $P < 0.20$  in Pearson's  
221 correlations were put into the multivariate stepwise linear regression models to  
222 identify factors that independently associated with FLI. We analyzed the impact of  
223 FLI on the prevalence of increased urinary albumin excretion and CKD. The  
224 unadjusted and multivariate-adjusted logistic regression analysis was used to assess  
225 the risk of prevalent increased urinary albumin excretion and CKD in relation to each  
226 quartile increase in FLI level. Variables considered as potential covariates and  
227 significant in the stepwise linear regression were put into multivariate-adjusted  
228 logistic regression analysis. Model 1 is unadjusted. Model 2 is adjusted for age. Model  
229 3 is adjusted for age, sex, current smoking status, current drinking status, physical  
230 activity, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL-C,  
231 fasting insulin, ALT and AST. Model 4 is adjusted for age, sex, BMI, WC, current  
232 smoking status, current drinking status, physical activity, systolic blood pressure  
233 (SBP), diastolic blood pressure (DBP), TG, LDL-C, fasting insulin, ALT, AST and  
234  $\gamma$ -GGT. Odds ratios (OR) and the corresponding 95% confidence intervals (95% CI)  
235 were calculated. Relationship of FLI level with albuminuria and CKD were also

236 explored in subgroups stratified by gender (men/women), age ( $\geq 60$ / $< 60$  years),  
237 degree of obesity (normal/overweight/obesity), current smoking (yes/no), current  
238 drinking (yes/no), hypertension (yes/no) and diabetes (yes/no). Tests for interaction  
239 were performed with including simultaneously each strata factor, the quartiles of FLI  
240 level and the respective interaction terms (strata factor multiplied by quartiles of FLI  
241 level) in the models.

242 All statistical tests were two-sided, and a P value  $< 0.05$  was considered  
243 statistically significant.

## 245 Results

### 246 Clinical characteristics of the study population

247 Among the 9,436 enrolled individuals, the mean age was  $55.9 \pm 8.0$  years. The  
248 median FLI was 19.1 with interquartile range 8.6 to 37.4. There were 620 (6.6%)  
249 subjects categorized as increased urinary albumin excretion and 753 (8.0%) subjects  
250 categorized as CKD, respectively. Table 1 shows the clinical and biochemical  
251 characteristics of the participants according to FLI quartiles. Participants with higher  
252 FLI level had elevated age, BMI, WC, SBP, DBP, TG, TC, LDL-C, FPG, fasting  
253 insulin, ALT, AST,  $\gamma$  - GGT and higher proportions of current smokers and current  
254 drinkers (all P for trend  $< 0.0001$ ). Those with higher FLI level also associated with  
255 decreased HDL-C and eGFR (all P for trend  $< 0.0001$ ).

### 256 Associations between FLI and metabolic risk factors

257 Analysis of Pearson's correlation showed that age, sex, BMI, WC, SBP, DBP, TG,

TC, HDL-C, LDL-C, FPG, fasting insulin, ALT, AST,  $\gamma$ -GGT and eGFR were significantly correlated with FLI level. Further multivariate stepwise linear regression showed that age, sex, BMI, WC, SBP, DBP, TG, LDL-C, fasting insulin, ALT, AST and  $\gamma$ -GGT were independent determinants for FLI level (Table 2).

**Associations of FLI with increased urinary albumin excretion and CKD**

As shown in Figure.1A, from the lowest quartile to the highest quartile of FLI level, the prevalence of increased urinary albumin excretion was 3.64%, 4.83%, 6.23% and 11.57%, respectively (P for trend < 0.0001). Strikingly, the prevalence of CKD also tended to increase with the elevated FLI quartile (Figure.1B, P for trend < 0.0001). As shown in Table 3, compared with participants in quartile 1 of FLI, univariate logistic regression analysis showed that participants in quartile 2, quartile 3 and quartile 4, respectively, have a significant correlation with increased odds of increased urinary albumin excretion and CKD (all P for trend < 0.0001). In multivariate logistic regression analyses (Model 3), the ORs of increased urinary albumin excretion for increasing FLI quartiles were 1.00 (reference), 0.96 (95% CI 0.66 - 1.39), 1.17 (95% CI 0.77 - 1.77) and 2.30 (95% CI 1.36 - 3.90). Similarly, the ORs of CKD for increasing FLI quartiles in Model 3 were 1.00 (reference), 1.00 (95% CI 0.71 - 1.40), 1.03 (95% CI 0.70 - 1.51) and 1.93 (95% CI 1.18 - 3.15), respectively (Table 3). The prevalence of increased urinary albumin excretion was 51.6% and 29.6% in FLI established NAFLD and non-NAFLD group (P < 0.0001). Similar trends were detected in the prevalence of CKD (NAFLD group: 49.9%; non-NAFLD group: 31.5%, P < 0.0001). Compared with participants in the non-NAFLD group,

those in NAFLD group had higher prevalence of increased urinary albumin excretion (OR 1.58, 95 % CI 1.18 - 2.13) and CKD (OR 1.39, 95 % CI 1.05 - 1.82) in multivariate logistic regression analyses.

### **Subgroups analysis of FLI with increased urinary albumin excretion and CKD**

As shown in Figure. 2 & 3, the associations of FLI level with increased urinary albumin excretion and CKD were not consistently the same in subgroups analyses. Significant relationship of FLI level with both increased urinary albumin excretion and CKD were detected in women, younger subjects (age less than 60 years), overweight subjects, non-current smokers, non-current drinkers and in those with hypertension or with diabetes (all  $P < 0.05$ ). In the subgroups analysis, no statistically significance of interaction term between quartiles of FLI and each strata factor was detected.

### **Discussion**

We evaluated the association between hepatic steatosis and kidney disease in a large population of middle-age Chinese subjects from the REACTION study. Presence of fatty liver assessed by FLI was associated with increased urinary albumin excretion and reduction of the eGFR in the present study. The association was independent of potential confounding risk factors. To our current knowledge, this is the largest population-based study to explore the association of FLI with both albuminuria and CKD in Asian population. Early intervention is of great importance for albuminuria and CKD, the present findings may just give insights into lipid

302 metabolism for prevention and early detection of the diseases.

303       The problem of obesity and NAFLD are now increasingly recognized in the Asian  
304 population. Prevalence of obesity was 7.9% (8.4% in males and 7.6% in females) in  
305 southern China, which has increased dramatically over the past several decades <sup>22</sup>.  
306 There is a strong correlation between established obesity and incidence of NAFLD.  
307 Pooled prevalence of NAFLD diagnosed by ultrasound, computed tomography scan  
308 and magnetic resonance was estimated to be 27.4% in subjects aged over 30 years  
309 from Asian countries <sup>23</sup>. Even among the non-obese Chinese, 8.9% developed  
310 NAFLD in five years from 2006 to 2011 <sup>24</sup>. Therefore, early and accurate diagnosis of  
311 NAFLD is of great importance. The best method for an accurate assessment and  
312 diagnosis of hepatic steatosis is histologic analysis of biopsies <sup>25</sup>. However, it is  
313 uneconomical to conduct liver biopsies especially by the fact of our large sample  
314 population. Hepatic ultrasonic examination is widely used in clinical practice and  
315 epidemiological studies in detecting fatty infiltration of the liver <sup>26 27</sup>. However, the  
316 noninvasive technique is not sensitive enough to detect mild steatosis and does not  
317 allow precise quantification of severity of steatosis in hepatic tissue <sup>28</sup>.

318       As another surrogate marker of histological fatty liver, FLI is defined as the  
319 accumulation of excessive liver fat <sup>29</sup>. Based on the former researches, FLI has been  
320 proven accurate in detecting fatty liver against liver ultrasound and demonstrating the  
321 presence of hepatic fat against magnetic resonance spectroscopy <sup>6 9 10 21</sup>. The  
322 superiority of this non-invasive assessment techniques is that a higher score will  
323 indicate a higher degree of steatosis in hepatic tissue. However, optimal cut-off point

of the FLI for evaluating liver fatty infiltration should be considered as it varied according to the study population<sup>21 30</sup>. Originally, FLI>60 was suggested to rule in NAFLD in Caucasian subjects. However, the optimal cut-off value of FLI for predicting NAFLD was different in Asian populations. In one recent study, Huang et al.<sup>21</sup> found that FLI could accurately identify NAFLD and the optimal cut-off point was 30 in middle-aged and elderly Chinese. FLI could also accurately identify ultrasonography fatty liver in a large scale population in Taiwan but with different optimal cut-off values, while an FLI>35 for males and >20 for females rule in NAFLD in their study<sup>30</sup>. Through the results of our research in Chinese subjects, further studies are therefore needed to externally discuss the optimal cut-off point of the FLI for predicting hepatic steatosis.

Detection and prevention of kidney disease progression and urinary albumin excretion is difficult to process in the early stage. Dyslipidemia is increasingly recognized as important pathogenic mechanism in deterioration of renal function. Recently, we conducted a clinical investigation to assess the associations of routine lipid measures with kidney disease in the same cohort. In the study, discordant associations of lipid parameters with renal insufficiency was detected while TG to HDL-C ratio is a better marker for evaluating increased urinary albumin excretion and CKD<sup>31</sup>. As one of the phenotype of dyslipidemia, the pathogenesises of hepatic steatosis is closely related to kidney disease with regard to insulin resistance and chronic inflammation<sup>32</sup>. Hepatokines, which are proteins secreted by hepatocytes, have been found to link to the induction of metabolic phenotypes through inter-organ

communication based on recent studies<sup>33</sup>. Because of the high prevalence and burden of the fatty liver disease, it is important to identify which patients are most likely to be exposed to early stage renal injury<sup>23</sup>. Consequently, we closely monitor the association of the hepatic steatosis predict by FLI with prevalent increased urinary albumin excretion and CKD.

Consistent with our findings, a previous study reported that hepatic steatosis evaluated by FLI might contribute to CKD development<sup>11</sup>. Elevated albuminuria is well known to be associated with increased risk for early diabetes renal damage, however, the identification and classification of kidney disease was assessed only by eGFR in that study. Moreover, 731 adults that underwent routine health evaluations were included in that study and the small sample size cannot better represent the whole population. By totally including 9,438 subjects and adopting both albuminuria and eGFR for renal damage assessment, data in our study demonstrated that the FLI is associated with kidney disease, which might be an efficient screening indicator for the early prevention of related diseases in Chinese subjects. Recently, an interesting study by Giorda C et al.<sup>34</sup> reported that NAFLD is a dynamic condition in type 2 diabetes subjects and about 5% Italian diabetic patients entering or leaving FLI assessed NAFLD status every year. They found that male sex and established organ damage, especially kidney function, were independent risk predictors for the dynamic NAFLD condition in a longitudinal 3-year analysis. As the similarity in traditional risk factors for both NAFLD and CKD, relationship between the prevalence of earlier stages of kidney damage and the incidence of NAFLD is complex. Longitudinal observation of

our cohort are needed to be carried out to determine whether such dynamic condition existed in the Chinese, especially in those with type 2 diabetes.

Alcohol consumption can profoundly disturb the lipid metabolism which have prominent effects on the hepatic tissue steatosis and insulin sensitivity<sup>35</sup>. However, potential health effects regarding alcohol consumption in this field is also worth attaching attention. A meta-analysis of intervention studies by Schrieks et al<sup>36</sup> showed that moderate alcohol intake could improve insulin sensitivity by decreasing fasting insulin level in women. Recently, a prospective cohort study found that alcohol consumption was consistently inversely associated with urinary albumin excretion and the risk of developing CKD<sup>37</sup>. Therefore, advice concerning alcohol consumption to subjects with low-grade hepatic tissue steatosis should consider the full range of benefits and risks, especially among those who drink moderately.

Some limitations of the study must be noted. Firstly, owing to the observational design of the current study, we should cautiously interpret the present findings as no causal inference can be drawn. Further prospective studies are therefore needed to determine the precise relationship between FLI and risk of renal diseases. Secondly, by including only Chinese subjects, the results of the present study might not be representative of other ethnic groups, especially for those in the developed or undeveloped countries. To some extent, however, the present study of Chinese population was still a convenience sample and selection bias is inevitable. Thirdly, when evaluating the findings of the present study, the results should be interpreted cautiously due to possible bias from using the indirect indicator FLI to assess fatty

390 liver disease. The calculated FLI may relate to various liver diseases with associated  
391 steatosis and not only NAFLD, despite the fact that metabolic disturbances make  
392 obesity related steatosis likely. The internal accuracy of FLI for evaluation hepatic  
393 steatosis should also be validated by using other techniques, before it can be  
394 employed for these purposes. Fourthly, we observed that FLI seem to play a different  
395 efficiency for kidney disease assessment in different stratifications. A significant  
396 association of FLI with increased urinary albumin excretion and CKD only detected  
397 in subjects without current alcohol consumption. Average daily alcohol intake  
398 influences the FLI and missing such data in the present study doesn't permit  
399 comparisons between and within alcoholic and nonalcoholic fatty liver disease  
400 groups. To better discriminate alcoholic fatty liver disease and non-alcoholic fatty  
401 liver disease, further studies need to clearly described the precise exposure of alcohol  
402 use by collecting histories of alcohol intake in a quantitative manner. Fifthly, viral  
403 hepatitis infection is one of the most serious infectious diseases worldwide, which  
404 can be associated with both liver and kidney disease. Recent survey data showed that  
405 the hepatitis B surface antigen and anti-hepatitis C virus-positive rates were already  
406 6.1% and 3.0% in China. Epidemiology of viral hepatitis infection by hepatitis B  
407 virus (HBV) and hepatitis C virus (HCV) serological testing, therefore, should be  
408 also be evaluate to strength the findings of the present study<sup>38</sup>. Sixthly, although a  
409 spectrum of covariates was included in the adjustment, other potential mediators  
410 such as daily energy and protein intake and medicine that influence the  
411 renin-angiotensin-system of the subjects, should also be considered in the present

study.

In conclusion, by including a large population based cohort, the present study provides evidence that increased FLI is independently associated with prevalence of albuminuria and CKD. Findings of the present study suggested us should pay more attention to albuminuria and eGFR variation in patients with dyslipidemia and fatty liver disease. Further prospective studies are necessary to verify our findings in external populations.

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**Figure legends**

**Figure. 1** Prevalence of increased urinary albumin excretion and CKD in different quartiles of FLI levels. (A) Increased urinary albumin excretion. (B) CKD.

**Figure. 2** Risk of prevalent increased urinary albumin excretion with each quartile increase of FLI levels in different subgroups.

**Figure. 3** Risk of prevalent CKD with each quartile increase of FLI levels in different subgroups.

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For peer review only

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**Table 1.** Characteristics of study population by FLI quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
n (%)	2360 (25.01)	2359 (24.99)	2359 (24.99)	2360 (25.01)	
Fatty liver index	5.00 (3.27 – 6.74)	13.23 (10.76 – 15.99)	26.96 (22.74 – 31.75)	54.71 (45.40 – 68.10)	
Urinary albumin to creatinine ratio (mg/g)	7.65 (5.59 – 11.12)	8.01 (5.64 – 11.71)	8.06 (5.73 – 11.83)*	8.93 (5.96 – 15.01)*#&	< 0.0001
Age (years)	54.3 ± 7.8	55.8 ± 7.9*	56.5 ± 7.9*#	56.9 ± 8.3*#	< 0.0001
Male [n (%)]	427 (18.09)	593 (25.17)	701 (29.72)	975 (41.31)	< 0.0001
BMI (kg/m <sup>2</sup> )	20.6 ± 2.0	22.9 ± 2.0*#&	24.4 ± 2.1*#	26.8 ± 3.5*#&	< 0.0001
WC (cm)	72.0 ± 5.8	79.3 ± 5.4*#&	84.1 ± 5.5*#	91.3 ± 8.5*#&	< 0.0001
SBP (mmHg)	118.6 ± 14.7	124.5 ± 15.9*#&	128.4 ± 15.8*#	132.5 ± 16.1*#&	< 0.0001
DBP (mmHg)	71.2 ± 9.1	74.2 ± 9.3*#&	76.5 ± 9.4*#	79.3 ± 9.8*#&	< 0.0001
Current smoking [n (%)]	169 (7.3)	202 (8.7)	227 (9.8)	335 (14.4)	< 0.0001
Current drinking [n (%)]	57 (2.5)	70 (3.0)	68 (2.9)	117 (5.1)	< 0.0001
TG (mmol/L)	0.85 (0.69 – 1.07)	1.12 (0.90 – 1.43)*#&	1.49 (1.13 – 1.94)*#	2.10 (1.56 – 3.01)*#&	< 0.0001
TC (mmol/L)	4.79 ± 1.24	5.16 ± 1.22*#&	5.35 ± 1.13*#	5.54 ± 1.17*#&	< 0.0001
HDL-C (mmol/L)	1.45 ± 0.41	1.37 ± 0.35*#&	1.29 ± 0.31*#	1.19 ± 0.28*#&	< 0.0001

LDL-C (mmol/L)	2.82 ± 0.90	3.19 ± 0.94 <sup>*&amp;</sup>	3.31 ± 0.91 <sup>*#</sup>	3.28 ± 0.95 <sup>*#</sup>	< 0.0001
FPG (mmol/L)	5.23 (4.89 – 5.61)	5.33 (4.95 – 5.80) <sup>*&amp;</sup>	5.47 (5.05 – 5.96) <sup>*#</sup>	5.73 (5.23 – 6.42) <sup>*#&amp;</sup>	< 0.0001
Fasting insulin (μIU/ml)	5.10 (3.90 – 6.50)	6.50 (5.00 – 8.40) <sup>*&amp;</sup>	7.90 (6.10 – 10.30) <sup>*#</sup>	10.50 (7.80 – 13.70) <sup>*#&amp;</sup>	< 0.0001
ALT (U/L)	10.0 (8.0 – 14.0)	12.0 (9.0 – 16.0) <sup>*&amp;</sup>	13.0 (10.0 – 17.0) <sup>*#</sup>	17.0 (12.0 – 24.0) <sup>*#&amp;</sup>	< 0.0001
AST (U/L)	17.0 (14.0 – 20.0)	18.0 (15.0 – 21.0) <sup>*&amp;</sup>	18.0 (15.0 – 22.0) <sup>*#</sup>	20.0 (17.0 – 25.0) <sup>*#&amp;</sup>	< 0.0001
γ-GGT (U/L)	14.0 (11.0 – 17.0)	18.0 (14.0 – 23.0) <sup>*&amp;</sup>	22.0 (17.0 – 29.0) <sup>*#</sup>	31.0 (23.0 – 47.0) <sup>*#&amp;</sup>	< 0.0001
Serum creatinine (μmol/L)	65.3 ± 15.5	68.8 ± 16.0 <sup>*&amp;</sup>	70.5 ± 16.0 <sup>*#</sup>	74.9 ± 17.2 <sup>*#&amp;</sup>	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	108.0 ± 25.4	102.5 ± 23.7 <sup>*&amp;</sup>	99.9 ± 19.6 <sup>*#</sup>	95.5 ± 19.5 <sup>*#&amp;</sup>	< 0.0001
Physical activity (MET-h/week)	24.0 (10.5 – 49.0)	24.0 (10.5 – 45.0)	23.0 (10.5 – 42.0)	21.0 (10.5 – 42.0) <sup>*</sup>	0.006
<p>1. Data were means ± SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.</p> <p>2. P for trend was calculated for the linear regression analysis tests across the groups. P values were for the ANOVA or <math>\chi^2</math> analyses across the groups.</p> <p>3. <sup>*</sup>P &lt; 0.05 compared with Quartile 1 of fatty liver index; <sup>#</sup>P &lt; 0.05 compared with Quartile 2 of fatty liver index; <sup>&amp;</sup>P &lt; 0.05 compared with Quartile 3 of fatty liver index.</p> <p>4. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyltransferase; eGFR, estimated glomerular filtration rate.</p>					

**Table 2.** Pearson's correlation and stepwise regression analysis of determinants of FLI

	r	P value	Standardized $\beta$	P value
Age (years)	0.12	< 0.0001	0.01	0.010
Sex (men=1, women=2)	-0.19	< 0.0001	-0.04	< 0.0001
BMI (kg/m <sup>2</sup> )	0.71	< 0.0001	0.30	< 0.0001
WC (cm)	0.78	< 0.0001	0.42	< 0.0001
Physical activity (MET-h/week)	-0.02	0.060	-	-
SBP (mmHg)	0.32	< 0.0001	0.01	0.006
DBP (mmHg)	0.32	< 0.0001	0.01	0.047
TG (mmol/L)	0.68	< 0.0001	0.42	< 0.0001
HDL-C (mmol/L)	-0.26	< 0.0001	-	-
LDL-C (mmol/L)	0.21	< 0.0001	0.06	< 0.0001
FPG (mmol/L)	0.22	< 0.0001	-	-
Fasting insulin ( $\mu$ IU/ml)	0.40	< 0.0001	0.01	0.0002
ALT (U/L)	0.20	< 0.0001	0.05	< 0.0001
AST (U/L)	0.15	< 0.0001	-0.03	< 0.0001
$\gamma$ -GGT (U/L)	0.35	< 0.0001	0.16	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	-0.19	< 0.0001	-	-

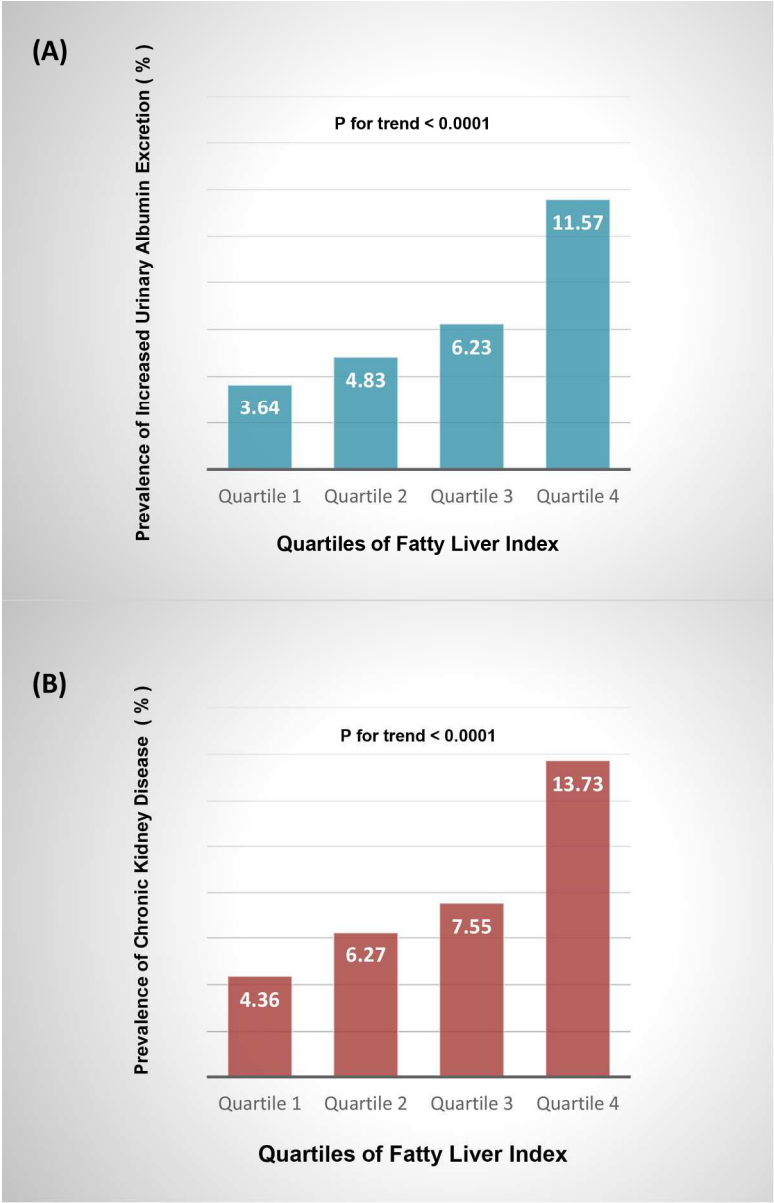
r, correlation coefficient;  $\beta$ , regression coefficient.

556

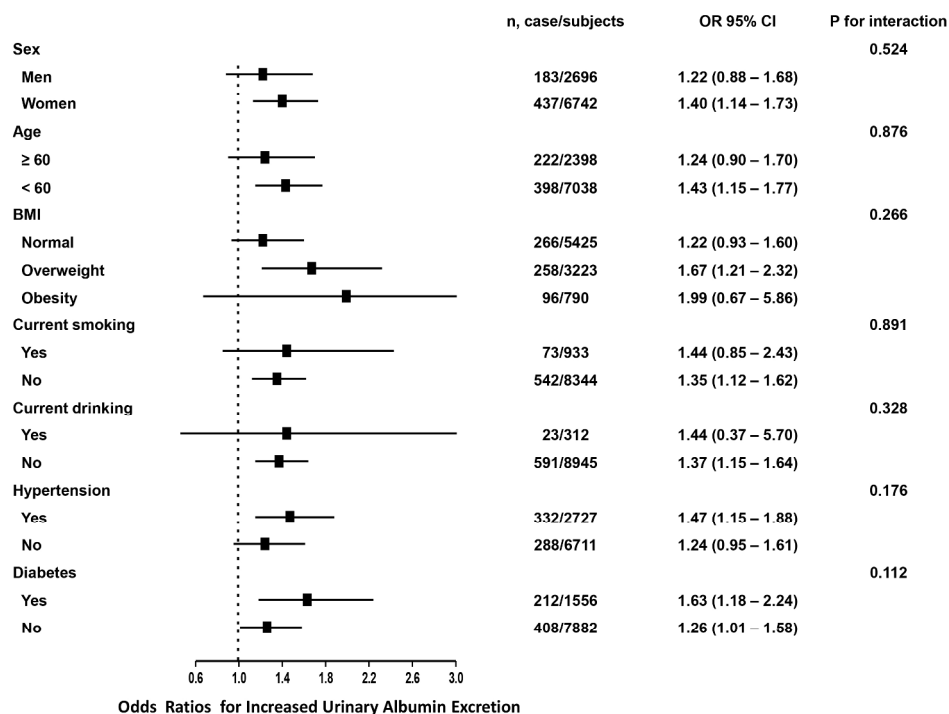
Table 3. The risk of prevalent albuminuria and CKD according to quartiles of FLI						
Increased urinary albumin excretion		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
	Model 1	1	1.34 (1.01 – 1.79)	1.76 (1.34 – 2.31)	3.46 (2.70 – 4.44)	< 0.0001
	Model 2	1	1.29 (0.97 – 1.72)	1.66 (1.27 – 2.19)	3.25 (2.53 – 4.17)	< 0.0001
	Model 3	1	0.94 (0.66 – 1.33)	1.13 (0.81 – 1.59)	2.22 (1.60 – 3.07)	< 0.0001
	Model 4	1	0.96 (0.66 – 1.39)	1.17 (0.77 – 1.77)	2.30 (1.36 – 3.90)	0.001
CKD	Model 1	1	1.47 (1.13 – 1.90)	1.79 (1.39 – 2.30)	3.49 (2.77 – 4.39)	< 0.0001
	Model 2	1	1.39 (1.07 – 1.80)	1.65 (1.28 – 2.12)	3.16 (2.51 – 3.99)	< 0.0001
	Model 3	1	0.99 (0.73 – 1.36)	1.03 (0.75 – 1.40)	1.95 (1.44 – 2.64)	< 0.0001
	Model 4	1	1.00 (0.71 – 1.40)	1.03 (0.70 – 1.51)	1.93 (1.18 – 3.15)	0.012
Data are odds ratios (95% confidence interval). Participants without increased urinary albumin excretion or CKD are defined as 0 and with increased urinary albumin excretion or CKD as 1. Model 1 is unadjusted. Model 2 is adjusted for age. Model 3 is adjusted for age, sex, current smoking status, current drinking status, physical activity, SBP, DBP, LDL-C, fasting insulin, ALT and AST. Model 4 is adjusted for age, sex, BMI, WC, current smoking status, current drinking status, physical activity, SBP, DBP, TG, LDL-C, fasting insulin, ALT,						

AST and  $\gamma$ -GGT.

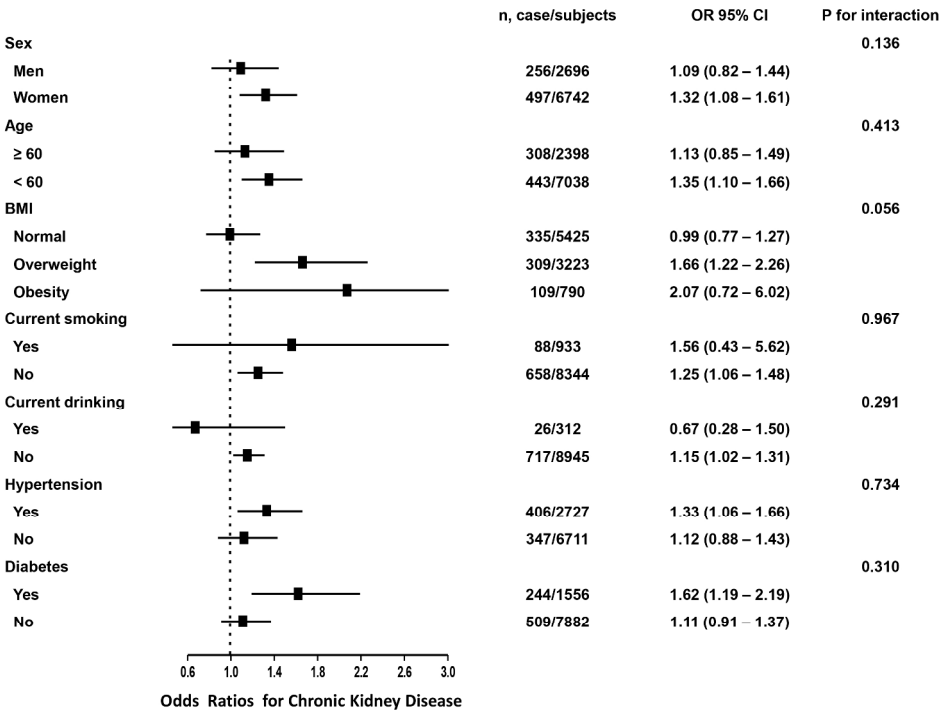
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145x226mm (300 x 300 DPI)



254x190mm (300 x 300 DPI)



254x190mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	L 1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	L 67-91
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	L 105-137
Objectives	3	State specific objectives, including any prespecified hypotheses	L 130-137
Methods			
Study design	4	Present key elements of study design early in the paper	L 141-146
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	L 141-179
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	L 141-153
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	L 155-207
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	L 193-207
Bias	9	Describe any efforts to address potential sources of bias	L 227-242
Study size	10	Explain how the study size was arrived at	L 143-146
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	L 210-219
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	L 210-242
		(b) Describe any methods used to examine subgroups and interactions	L 236-239
		(c) Explain how missing data were addressed	N.A.
		(d) If applicable, describe analytical methods taking account of sampling strategy	N.A.
		(e) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	L 248-256
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	L 248-262
		(b) Indicate number of participants with missing data for each variable of	L 248-

		interest	292
Outcome data	15*	Report numbers of outcome events or summary measures	L 264-283
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	L 264-283
		(b) Report category boundaries when continuous variables were categorized	L 210-219
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	L 285-292
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	L 295-303
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	L 374-403
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	L 329-373
Generalisability	21	Discuss the generalisability (external validity) of the study results	L 377-381
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	L 47-59

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Fatty liver index, albuminuria and the association with chronic kidney disease: a population-based study in China

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Manuscripts

**1 Fatty liver index, albuminuria and the association with chronic**  
**2 kidney disease: a population-based study in China**

**3**  
**4 Kan Sun<sup>1#</sup>, Diaozhu Lin<sup>1#</sup>, Feng Li<sup>1</sup>, Yiqin Qi<sup>1</sup>, Wanting Feng<sup>1</sup>, Li Yan<sup>1</sup>,**  
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**Running title:** Fatty liver index and kidney disease

## **Statement of authorship**

All authors believe that the manuscript represents valid work and have reviewed and approved the final version. The work has not been published previously, and not under consideration for publication elsewhere, in part or in whole.

## **The author contribution lists**

Conceived and designed the experiments: Y. L. and K. S.

Performed the experiments: F. L., Y. Q., W. F., C. C., K. S. and D. L.

Analyzed the data: K. S. and M. R.

Wrote the manuscript: K.S. and D. L.

## **Data Sharing Statement**

The work described was original research that has not been published previously, and not under consideration for publication elsewhere, in part or in whole. All authors believe that the manuscript represents valid work and have reviewed and approved the final version. Main document data and additional unpublished data from the study are available by sending Email to lizyhenu@163.com with proper purposes.

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59 preparation of the manuscript.

60

61 **Conflict of interests**

62 The authors have declared that no competing interests exist.

63

64

65

66 **ABSTRACT**

67 **Objectives:** The effects of lipid metabolism disorder on the renal damage have drawn  
68 much attention. By using the fatty liver index (FLI) as a validated indicator of hepatic  
69 steatosis, this study aims at provide insight about the possible links between fatty liver  
70 and development of chronic kidney disease (CKD).

71 **Setting:** hospital.

72 **Participants:** We performed a population-based study in 9,436 subjects aged 40 years  
73 or older.

74 **Primary and secondary outcome measures:** FLI is calculated by using an algorithm  
75 based on body mass index (BMI), waist circumference (WC), triglycerides (TG) and  
76  $\gamma$ -glutamyltransferase ( $\gamma$ -GGT). Increased urinary albumin excretion was defined  
77 according to the urinary albumin-to-creatinine ratio ranges greater or equal than 30  
78 mg/g. CKD was defined as estimated glomerular filtration rate (eGFR) less than 60  
79 mL/min per 1.73 m<sup>2</sup> or presence of albuminuria.

80 **Results:** There were 620 (6.6%) subjects categorized as increased urinary albumin  
81 excretion and 753 (8.0%) subjects categorized as CKD. Participants with higher FLI  
82 had increased age, blood pressure, low-density lipoprotein cholesterol, fasting plasma  
83 glucose, fasting insulin and decreased eGFR level. Prevalence of increased urinary  
84 albumin excretion and CKD tended to increase with the elevated FLI quartiles. In  
85 logistic regression analysis, compared with subjects in the lowest quartile of FLI, the  
86 adjusted odds ratios (ORs) in the highest quartile was 2.30 [95% confidence interval

(CI), 1.36 - 3.90] for increased urinary albumin excretion and 1.93 (95% CI, 1.18 - 3.15) for CKD.

**Conclusion:** Hepatic steatosis evaluating by FLI is independently associated with increased urinary albumin excretion and prevalence of CKD in middle-aged and elderly Chinese.

**Keywords:** Fatty liver index; Hepatic steatosis; Increased urinary albumin excretion; Chronic kidney disease

**Strengths and Limitations**

1. The study was performed in a large population-based cohort in 9,436 Chinese subjects.
2. Findings of the study may be applied to the majority of patients in general practice with suspected hepatic steatosis.
3. Results should be interpreted cautiously due to the observational design of the current study.

## 104 Introduction

105 Chronic kidney disease (CKD) has become one of the leading public health  
106 problem world-wide <sup>1</sup>. Recent national survey conducted between 2007 and 2010  
107 reports that the prevalence of CKD was 10.8%, representing an estimated 119.5  
108 million patients in China are with chronic kidney damage <sup>2</sup>. In addition to CKD, an  
109 increasing number of studies have provided substantial evidence of albuminuria as a  
110 risk factor for future cardiovascular events <sup>3</sup>. Both renal and cardiovascular diseases  
111 sharing similar traditional risk factors, such as lipid metabolism disorder, could have  
112 particularly broad implications for the outcome of cardiovascular morbidity and  
113 mortality.

114 Association of hepatic steatosis with CKD development and its impact on the  
115 reduction of the estimated glomerular filtration rate (eGFR) have been extensively  
116 investigated over the past decade <sup>4</sup>. The substantial evidence linked hepatic steatosis  
117 to the increased risk and severity of CKD, which may be a target for the prevention  
118 and treatment of the disease <sup>5</sup>. As a convenient scoring system for the presence of  
119 hepatic lipid deposits, the fatty liver index (FLI) is a surrogate steatosis biomarker  
120 developed in a cohort of patients from the general population <sup>6</sup>. Compared with other  
121 techniques for evaluating hepatic steatosis, FLI is simple to obtain as body mass index  
122 (BMI), waist circumference (WC), triglycerides (TG) and  $\gamma$ -glutamyltransferase  
123 ( $\gamma$ -GGT) are routine measurements in clinical practice. Previous studies have  
124 demonstrated that FLI could determine fatty liver disease, incident type 2 diabetes and  
125 incident hypertension with considerable accuracy <sup>6-8</sup>. Moreover, FLI is associated with

126 insulin resistance early atherosclerosis and risk of coronary heart disease, which could  
127 help physicians early detect subjects of greater cardiovascular risk and select patients  
128 for intensified lifestyle counseling<sup>9 10</sup>.

129 Clarifying the association of FLI with albuminuria and prevalent CKD would  
130 probably shed light on the prevention and preemptive treatment of related diseases.  
131 Recently, a cross-sectional study was conducted to investigate the association between  
132 FLI and CKD by recruiting adults undergoing a health check-up<sup>11</sup>. However, by  
133 including only 731 subjects, the study did not evaluate the association between FLI  
134 and albuminuria, either. Therefore, we analyzed data from a community-based  
135 Chinese population to comprehensively look into the relationship of FLI with both  
136 increased urinary albumin excretion and CKD.

137

138 **Subjects and methods**

139 **Study population and design**

140 We performed a cross-sectional study in a community in Guangzhou, China from  
141 June to November, 2011. The study population was from the REACTION study and  
142 details of this study have been published previously<sup>12-14</sup>. During the recruiting phase,  
143 a total of 10,104 residents aged 40 years or older were invited to participate by  
144 examination notices or home visits. In total, 9,916 subjects signed the consent form  
145 and agreed to participate in the survey. The participation rate was 98.1%. The subjects  
146 who failed to provide information (BMI: n=206; WC: n=62; TG: n=23;  $\gamma$ -GGT: n=38;  
147 or urinary albumin-to-creatinine ratio [ACR]: n=149) were excluded from the

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3  
4 148 analyses. Accordingly, a total of 9,438 eligible individuals were included in the final  
5  
6 149 data analyses. The study protocol was approved by the Institutional Review Board of  
7  
8 150 the Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University and was in  
9  
10  
11 151 accordance with the principle of the Helsinki Declaration II. Written informed consent  
12  
13 152 was obtained from each participant before data collection.  
14

### 15 153 **Clinical and biochemical measurements**

16  
17  
18 154 We collected information on lifestyle factors, sociodemographic characteristics  
19  
20  
21 155 and family history by using a standard questionnaire. Smoking or drinking habit was  
22  
23 156 classified as 'never', 'current' (smoking or drinking regularly in the past 6 months) or  
24  
25 157 'ever' (cessation of smoking or drinking more than 6 months)<sup>15</sup>. A short form of the  
26  
27  
28 158 International Physical Activity Questionnaire (IPAQ) was used to estimate physical  
29  
30  
31 159 activity at leisure time by adding questions on frequency and duration of moderate or  
32  
33 160 vigorous activities and walking<sup>16</sup>. Separate metabolic equivalent hours per week  
34  
35 161 (MET-h/week) were calculated for evaluation of total physical activity.  
36

37  
38 162 All participants completed anthropometrical measurements with the assistance  
39  
40  
41 163 of trained staff by using standard protocols. Three times consecutively blood pressure  
42  
43 164 measurements by the same observer in a 5-minute interval were obtained by an  
44  
45 165 automated electronic device (OMRON, Omron Company, China). The average of  
46  
47  
48 166 three measurements of blood pressure was used for analysis. Body height and body  
49  
50  
51 167 weight were recorded to the nearest 0.1 cm and 0.1 kg while participants were  
52  
53 168 wearing light indoor clothing without shoes. BMI was calculated as weight in  
54  
55 169 kilograms divided by height in meters squared ( $\text{kg/m}^2$ ). Obesity was defined as BMI  
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60

170 equal or greater than 28 and overweight was defined as BMI equal or greater than 24  
171 and less than 28<sup>17</sup>. WC was measured at the umbilical level with participant in  
172 standing position, at the end of gentle expiration.

173 Venous blood samples were collected for laboratory tests after an overnight  
174 fasting of at least 10 hours. Measurement of fasting plasma glucose (FPG), fasting  
175 serum insulin, TG, total cholesterol (TC), high-density lipoprotein cholesterol  
176 (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine,  $\gamma$ -GGT, aspartate  
177 aminotransferase (AST) and alanine aminotransferase (ALT) was done using an  
178 autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA).

179 As surrogate marker of hepatic steatosis, FLI was analyzed based on BMI, WC,  
180 TG, and  $\gamma$ -GGT, which has been validated against liver ultrasound in the general  
181 population and has been proven accurate in detecting fatty liver<sup>6 10</sup>. FLI is calculated  
182 as:  $FLI = (e^{0.953 * \log_e(TG) + 0.139 * BMI + 0.718 * \log_e(GGT) + 0.053 * WC - 15.745}) / (1$   
183  $+ e^{0.953 * \log_e(TG) + 0.139 * BMI + 0.718 * \log_e(GGT) + 0.053 * WC - 15.745}) * 100$ . The  
184 abbreviated Modification of Diet in Renal Disease (MDRD) formula recalibrated for  
185 Chinese population was used to calculate estimated glomerular filtration rate (GFR)  
186 expressed in mL/min per 1.73 m<sup>2</sup> using a formula of  $eGFR = 175 \times [\text{serum creatinine}$   
187  $\times 0.011]^{-1.234} \times [\text{age}]^{-0.179} \times [0.79 \text{ if female}]$ , where serum creatinine was expressed as  
188  $\mu\text{mol/L}$ <sup>18</sup>. Diabetes was diagnosed according to the 1999 World Health Organization  
189 diagnostic criteria<sup>19</sup>.

190 **Definition of increased urinary albumin excretion, chronic kidney disease and**  
191 **non-alcoholic fatty liver disease (NAFLD)**

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3  
4 192 Definitions of abnormalities in albumin excretion were according to the latest  
5  
6 193 guidelines of American Diabetes Association's Standards of Medical Care<sup>20</sup>. The first  
7  
8 194 morning spot urine samples were collected for assessing the ACR. Urine albumin and  
9  
10  
11 195 creatinine were measured by chemiluminescence immunoassay (Siemens Immulite  
12  
13 196 2000, United States) and the Jaffe's kinetic method (Biobase-Crystal, Jinan, China)  
14  
15  
16 197 on the automatic analyzer, respectively. ACR was calculated by dividing the urinary  
17  
18 198 albumin concentrations by the urinary creatinine concentrations and expressed in  
19  
20 199 mg/g. The primary and secondary outcome measures were increased urinary albumin  
21  
22  
23 200 excretion and chronic kidney disease (CKD), respectively. Increased urinary albumin  
24  
25  
26 201 excretion was defined according to the ACR ranges greater or equal than 30 mg/g.  
27  
28 202 Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min per 1.73 m<sup>2</sup>  
29  
30  
31 203 or presence of albuminuria (ACR greater or equal than 30 mg/g). The optimal cutoff  
32  
33 204 value of FLI for predicting NAFLD was 30 in Asian populations<sup>21</sup>. Therefore, we  
34  
35 205 classified the study population in non-current drinking group into NAFLD group (FLI  
36  
37  
38 206  $\geq 30$ ) and non-NAFLD group (FLI < 30).

## 207 208 **Statistical analysis**

209 Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary,  
210 NC, USA). Continuous variables were presented as means  $\pm$  standard deviation (SD)  
211 except for skewed variables, which were presented as medians (interquartile ranges).  
212 Categorical variables were expressed as numbers (proportions). FLI, FPG, TG, ALT,  
213 AST,  $\gamma$ -GGT and MET-h/week were logarithmically transformed before analysis due

214 to a non-normal distribution. FLI was presented as quartiles and linear regression  
215 analysis was used to test for trend across groups. Differences among groups were  
216 tested by one-way ANOVA and *post hoc* comparisons were performed by using  
217 Bonferroni correction. Comparisons between categorical variables were performed  
218 with the  $\chi^2$  test.

219 Pearson's correlations were performed to test the correlations between FLI and  
220 the risk factors for kidney disease. Variables significant at  $P < 0.20$  in Pearson's  
221 correlations were put into the multivariate stepwise linear regression models to  
222 identify factors that independently associated with FLI. We analyzed the impact of  
223 FLI on the prevalence of increased urinary albumin excretion and CKD. The  
224 unadjusted and multivariate-adjusted logistic regression analysis was used to assess  
225 the risk of prevalent increased urinary albumin excretion and CKD in relation to each  
226 quartile increase in FLI level. Variables considered as potential covariates and  
227 significant in the stepwise linear regression were put into multivariate-adjusted  
228 logistic regression analysis. Model 1 is unadjusted. Model 2 is adjusted for age. Model  
229 3 is adjusted for age, sex, current smoking status, current drinking status, physical  
230 activity, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL-C,  
231 fasting insulin, ALT and AST. Model 4 is adjusted for age, sex, BMI, WC, current  
232 smoking status, current drinking status, physical activity, systolic blood pressure  
233 (SBP), diastolic blood pressure (DBP), TG, LDL-C, fasting insulin, ALT, AST and  
234  $\gamma$ -GGT. Odds ratios (OR) and the corresponding 95% confidence intervals (95% CI)  
235 were calculated. Relationship of FLI level with albuminuria and CKD were also

236 explored in subgroups stratified by gender (men/women), age ( $\geq 60$ / $< 60$  years),  
237 degree of obesity (normal/overweight/obesity), current smoking (yes/no), current  
238 drinking (yes/no), hypertension (yes/no) and diabetes (yes/no). Tests for interaction  
239 were performed with including simultaneously each strata factor, the quartiles of FLI  
240 level and the respective interaction terms (strata factor multiplied by quartiles of FLI  
241 level) in the models.

242 All statistical tests were two-sided, and a P value  $< 0.05$  was considered  
243 statistically significant.

## 245 Results

### 246 Clinical characteristics of the study population

247 Among the 9,436 enrolled individuals, the mean age was  $55.9 \pm 8.0$  years. The  
248 median FLI was 19.1 with interquartile range 8.6 to 37.4. There were 620 (6.6%)  
249 subjects categorized as increased urinary albumin excretion and 753 (8.0%) subjects  
250 categorized as CKD, respectively. Table 1 shows the clinical and biochemical  
251 characteristics of the participants according to FLI quartiles. Participants with higher  
252 FLI level had elevated age, BMI, WC, SBP, DBP, TG, TC, LDL-C, FPG, fasting  
253 insulin, ALT, AST,  $\gamma$  - GGT and higher proportions of current smokers and current  
254 drinkers (all P for trend  $< 0.0001$ ). Those with higher FLI level also associated with  
255 decreased HDL-C and eGFR (all P for trend  $< 0.0001$ ).

### 256 Associations between FLI and metabolic risk factors

257 Analysis of Pearson's correlation showed that age, sex, BMI, WC, SBP, DBP, TG,

TC, HDL-C, LDL-C, FPG, fasting insulin, ALT, AST,  $\gamma$ -GGT and eGFR were significantly correlated with FLI level. Further multivariate stepwise linear regression showed that age, sex, BMI, WC, SBP, DBP, TG, LDL-C, fasting insulin, ALT, AST and  $\gamma$ -GGT were independent determinants for FLI level (Table 2).

**Associations of FLI with increased urinary albumin excretion and CKD**

As shown in Figure.1A, from the lowest quartile to the highest quartile of FLI level, the prevalence of increased urinary albumin excretion was 3.64%, 4.83%, 6.23% and 11.57%, respectively (P for trend < 0.0001). Strikingly, the prevalence of CKD also tended to increase with the elevated FLI quartile (Figure.1B, P for trend < 0.0001). As shown in Table 3, compared with participants in quartile 1 of FLI, univariate logistic regression analysis showed that participants in quartile 2, quartile 3 and quartile 4, respectively, have a significant correlation with increased odds of increased urinary albumin excretion and CKD (all P for trend < 0.0001). In multivariate logistic regression analyses (Model 3), the ORs of increased urinary albumin excretion for increasing FLI quartiles were 1.00 (reference), 0.96 (95% CI 0.66 - 1.39), 1.17 (95% CI 0.77 - 1.77) and 2.30 (95% CI 1.36 - 3.90). Similarly, the ORs of CKD for increasing FLI quartiles in Model 3 were 1.00 (reference), 1.00 (95% CI 0.71 - 1.40), 1.03 (95% CI 0.70 - 1.51) and 1.93 (95% CI 1.18 - 3.15), respectively (Table 3). The prevalence of increased urinary albumin excretion was 51.6% and 29.6% in FLI established NAFLD and non-NAFLD group (P < 0.0001). Similar trends were detected in the prevalence of CKD (NAFLD group: 49.9%; non-NAFLD group: 31.5%, P < 0.0001). Compared with participants in the non-NAFLD group,

those in NAFLD group had higher prevalence of increased urinary albumin excretion (OR 1.58, 95 % CI 1.18 - 2.13) and CKD (OR 1.39, 95 % CI 1.05 - 1.82) in multivariate logistic regression analyses.

### **Subgroups analysis of FLI with increased urinary albumin excretion and CKD**

As shown in Figure. 2 & 3, the associations of FLI level with increased urinary albumin excretion and CKD were not consistently the same in subgroups analyses. Significant relationship of FLI level with both increased urinary albumin excretion and CKD were detected in women, younger subjects (age less than 60 years), overweight subjects, non-current smokers, non-current drinkers and in those with hypertension or with diabetes (all  $P < 0.05$ ). In the subgroups analysis, no statistically significance of interaction term between quartiles of FLI and each strata factor was detected.

### **Discussion**

We evaluated the association between hepatic steatosis and kidney disease in a large population of middle-age Chinese subjects from the REACTION study. Presence of fatty liver assessed by FLI was associated with increased urinary albumin excretion and reduction of the eGFR in the present study. The association was independent of potential confounding risk factors. To our current knowledge, this is the largest population-based study to explore the association of FLI with both albuminuria and CKD in Asian population. Early intervention is of great importance for albuminuria and CKD, the present findings may just give insights into lipid

302 metabolism for prevention and early detection of the diseases.

303       The problem of obesity and NAFLD are now increasingly recognized in the Asian  
304 population. Prevalence of obesity was 7.9% (8.4% in males and 7.6% in females) in  
305 southern China, which has increased dramatically over the past several decades <sup>22</sup>.  
306 There is a strong correlation between established obesity and incidence of NAFLD.  
307 Pooled prevalence of NAFLD diagnosed by ultrasound, computed tomography scan  
308 and magnetic resonance was estimated to be 27.4% in subjects aged over 30 years  
309 from Asian countries <sup>23</sup>. Even among the non-obese Chinese, 8.9% developed  
310 NAFLD in five years from 2006 to 2011 <sup>24</sup>. Therefore, early and accurate diagnosis of  
311 NAFLD is of great importance. The best method for an accurate assessment and  
312 diagnosis of hepatic steatosis is histologic analysis of biopsies <sup>25</sup>. However, it is  
313 uneconomical to conduct liver biopsies especially by the fact of our large sample  
314 population. Hepatic ultrasonic examination is widely used in clinical practice and  
315 epidemiological studies in detecting fatty infiltration of the liver <sup>26 27</sup>. However, the  
316 noninvasive technique is not sensitive enough to detect mild steatosis and does not  
317 allow precise quantification of severity of steatosis in hepatic tissue <sup>28</sup>.

318       As another surrogate marker of histological fatty liver, FLI is defined as the  
319 accumulation of excessive liver fat <sup>29</sup>. Based on the former researches, FLI has been  
320 proven accurate in detecting fatty liver against liver ultrasound and demonstrating the  
321 presence of hepatic fat against magnetic resonance spectroscopy <sup>6 9 10 21</sup>. The  
322 superiority of this non-invasive assessment techniques is that a higher score will  
323 indicate a higher degree of steatosis in hepatic tissue. However, optimal cut-off point

of the FLI for evaluating liver fatty infiltration should be considered as it varied according to the study population<sup>21 30</sup>. Originally, FLI>60 was suggested to rule in NAFLD in Caucasian subjects. However, the optimal cut-off value of FLI for predicting NAFLD was different in Asian populations. In one recent study, Huang et al.<sup>21</sup> found that FLI could accurately identify NAFLD and the optimal cut-off point was 30 in middle-aged and elderly Chinese. FLI could also accurately identify ultrasonography fatty liver in a large scale population in Taiwan but with different optimal cut-off values, while an FLI>35 for males and >20 for females rule in NAFLD in their study<sup>30</sup>. Through the results of our research in Chinese subjects, further studies are therefore needed to externally discuss the optimal cut-off point of the FLI for predicting hepatic steatosis.

Detection and prevention of kidney disease progression and urinary albumin excretion is difficult to process in the early stage. Dyslipidemia is increasingly recognized as important pathogenic mechanism in deterioration of renal function. Recently, we conducted a clinical investigation to assess the associations of routine lipid measures with kidney disease in the same cohort. In the study, discordant associations of lipid parameters with renal insufficiency was detected while TG to HDL-C ratio is a better marker for evaluating increased urinary albumin excretion and CKD<sup>31</sup>. As one of the phenotype of dyslipidemia, the pathogenesises of hepatic steatosis is closely related to kidney disease with regard to insulin resistance and chronic inflammation<sup>32</sup>. Hepatokines, which are proteins secreted by hepatocytes, have been found to link to the induction of metabolic phenotypes through inter-organ

communication based on recent studies<sup>33</sup>. Because of the high prevalence and burden of the fatty liver disease, it is important to identify which patients are most likely to be exposed to early stage renal injury<sup>23</sup>. Consequently, we closely monitor the association of the hepatic steatosis predict by FLI with prevalent increased urinary albumin excretion and CKD.

Consistent with our findings, a previous study reported that hepatic steatosis evaluated by FLI might contribute to CKD development<sup>11</sup>. Elevated albuminuria is well known to be associated with increased risk for early diabetes renal damage, however, the identification and classification of kidney disease was assessed only by eGFR in that study. Moreover, 731 adults that underwent routine health evaluations were included in that study and the small sample size cannot better represent the whole population. By totally including 9,438 subjects and adopting both albuminuria and eGFR for renal damage assessment, data in our study demonstrated that the FLI is associated with kidney disease, which might be an efficient screening indicator for the early prevention of related diseases in Chinese subjects. Recently, an interesting study by Giorda C et al.<sup>34</sup> reported that NAFLD is a dynamic condition in type 2 diabetes subjects and about 5% Italian diabetic patients entering or leaving FLI assessed NAFLD status every year. They found that male sex and established organ damage, especially kidney function, were independent risk predictors for the dynamic NAFLD condition in a longitudinal 3-year analysis. As the similarity in traditional risk factors for both NAFLD and CKD, relationship between the prevalence of earlier stages of kidney damage and the incidence of NAFLD is complex. Longitudinal observation of

our cohort are needed to be carried out to determine whether such dynamic condition existed in the Chinese, especially in those with type 2 diabetes.

Alcohol consumption can profoundly disturb the lipid metabolism which have prominent effects on the hepatic tissue steatosis and insulin sensitivity<sup>35</sup>. However, potential health effects regarding alcohol consumption in this field is also worth attaching attention. A meta-analysis of intervention studies by Schrieks et al<sup>36</sup>. showed that moderate alcohol intake could improve insulin sensitivity by decreasing fasting insulin level in women. Recently, a prospective cohort study found that alcohol consumption was consistently inversely associated with urinary albumin excretion and the risk of developing CKD<sup>37</sup>. Therefore, advice concerning alcohol consumption to subjects with low-grade hepatic tissue steatosis should consider the full range of benefits and risks, especially among those who drink moderately.

Some limitations of the study must be noted. Firstly, owing to the observational design of the current study, we should cautiously interpret the present findings as no causal inference can be drawn. Further prospective studies are therefore needed to determine the precise relationship between FLI and risk of renal diseases. Secondly, by including only Chinese subjects, the results of the present study might not be representative of other ethnic groups, especially for those in the developed or undeveloped countries. To some extent, however, the present study of Chinese population was still a convenience sample and selection bias is inevitable. Thirdly, when evaluating the findings of the present study, the results should be interpreted cautiously due to possible bias from using the indirect indicator FLI to assess fatty

390 liver disease. The calculated FLI may relate to various liver diseases with associated  
391 steatosis and not only NAFLD, despite the fact that metabolic disturbances make  
392 obesity related steatosis likely. The internal accuracy of FLI for evaluation hepatic  
393 steatosis should also be validated by using other techniques, before it can be  
394 employed for these purposes. Fourthly, we observed that FLI seem to play a different  
395 efficiency for kidney disease assessment in different stratifications. A significant  
396 association of FLI with increased urinary albumin excretion and CKD only detected  
397 in subjects without current alcohol consumption. Average daily alcohol intake  
398 influences the FLI and missing such data in the present study doesn't permit  
399 comparisons between and within alcoholic and nonalcoholic fatty liver disease  
400 groups. To better discriminate alcoholic fatty liver disease and non-alcoholic fatty  
401 liver disease, further studies need to clearly described the precise exposure of alcohol  
402 use by collecting histories of alcohol intake in a quantitative manner. Fifthly, viral  
403 hepatitis infection is one of the most serious infectious diseases worldwide, which  
404 can be associated with both liver and kidney disease. Recent survey data showed that  
405 the hepatitis B surface antigen and anti-hepatitis C virus-positive rates were already  
406 6.1% and 3.0% in China. Epidemiology of viral hepatitis infection by hepatitis B  
407 virus (HBV) and hepatitis C virus (HCV) serological testing, therefore, should be  
408 also be evaluate to strength the findings of the present study<sup>38</sup>. Sixthly, although a  
409 spectrum of covariates was included in the adjustment, other potential mediators  
410 such as daily energy and protein intake and medicine that influence the  
411 renin-angiotensin-system of the subjects, should also be considered in the present

study.

In conclusion, by including a large population based cohort, the present study provides evidence that increased FLI is independently associated with prevalence of albuminuria and CKD. Findings of the present study suggested us should pay more attention to albuminuria and eGFR variation in patients with dyslipidemia and fatty liver disease. Further prospective studies are necessary to verify our findings in external populations.

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**Figure legends**

**Figure. 1** Prevalence of increased urinary albumin excretion and CKD in different quartiles of FLI levels. (A) Increased urinary albumin excretion. (B) CKD.

**Figure. 2** Risk of prevalent increased urinary albumin excretion with each quartile increase of FLI levels in different subgroups.

**Figure. 3** Risk of prevalent CKD with each quartile increase of FLI levels in different subgroups.

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**Table 1.** Characteristics of study population by FLI quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
n (%)	2360 (25.01)	2359 (24.99)	2359 (24.99)	2360 (25.01)	
Fatty liver index	5.00 (3.27 – 6.74)	13.23 (10.76 – 15.99)	26.96 (22.74 – 31.75)	54.71 (45.40 – 68.10)	
Urinary albumin to creatinine ratio (mg/g)	7.65 (5.59 – 11.12)	8.01 (5.64 – 11.71)	8.06 (5.73 – 11.83)*	8.93 (5.96 – 15.01)*#&	< 0.0001
Age (years)	54.3 ± 7.8	55.8 ± 7.9*	56.5 ± 7.9*#	56.9 ± 8.3*#	< 0.0001
Male [n (%)]	427 (18.09)	593 (25.17)	701 (29.72)	975 (41.31)	< 0.0001
BMI (kg/m <sup>2</sup> )	20.6 ± 2.0	22.9 ± 2.0*#&	24.4 ± 2.1*#	26.8 ± 3.5*#&	< 0.0001
WC (cm)	72.0 ± 5.8	79.3 ± 5.4*#&	84.1 ± 5.5*#	91.3 ± 8.5*#&	< 0.0001
SBP (mmHg)	118.6 ± 14.7	124.5 ± 15.9*#&	128.4 ± 15.8*#	132.5 ± 16.1*#&	< 0.0001
DBP (mmHg)	71.2 ± 9.1	74.2 ± 9.3*#&	76.5 ± 9.4*#	79.3 ± 9.8*#&	< 0.0001
Current smoking [n (%)]	169 (7.3)	202 (8.7)	227 (9.8)	335 (14.4)	< 0.0001
Current drinking [n (%)]	57 (2.5)	70 (3.0)	68 (2.9)	117 (5.1)	< 0.0001
TG (mmol/L)	0.85 (0.69 – 1.07)	1.12 (0.90 – 1.43)*#&	1.49 (1.13 – 1.94)*#	2.10 (1.56 – 3.01)*#&	< 0.0001
TC (mmol/L)	4.79 ± 1.24	5.16 ± 1.22*#&	5.35 ± 1.13*#	5.54 ± 1.17*#&	< 0.0001
HDL-C (mmol/L)	1.45 ± 0.41	1.37 ± 0.35*#&	1.29 ± 0.31*#	1.19 ± 0.28*#&	< 0.0001

LDL-C (mmol/L)	2.82 ± 0.90	3.19 ± 0.94 <sup>*&amp;</sup>	3.31 ± 0.91 <sup>*#</sup>	3.28 ± 0.95 <sup>*#</sup>	< 0.0001
FPG (mmol/L)	5.23 (4.89 – 5.61)	5.33 (4.95 – 5.80) <sup>*&amp;</sup>	5.47 (5.05 – 5.96) <sup>*#</sup>	5.73 (5.23 – 6.42) <sup>*#&amp;</sup>	< 0.0001
Fasting insulin (μIU/ml)	5.10 (3.90 – 6.50)	6.50 (5.00 – 8.40) <sup>*&amp;</sup>	7.90 (6.10 – 10.30) <sup>*#</sup>	10.50 (7.80 – 13.70) <sup>*#&amp;</sup>	< 0.0001
ALT (U/L)	10.0 (8.0 – 14.0)	12.0 (9.0 – 16.0) <sup>*&amp;</sup>	13.0 (10.0 – 17.0) <sup>*#</sup>	17.0 (12.0 – 24.0) <sup>*#&amp;</sup>	< 0.0001
AST (U/L)	17.0 (14.0 – 20.0)	18.0 (15.0 – 21.0) <sup>*&amp;</sup>	18.0 (15.0 – 22.0) <sup>*#</sup>	20.0 (17.0 – 25.0) <sup>*#&amp;</sup>	< 0.0001
γ-GGT (U/L)	14.0 (11.0 – 17.0)	18.0 (14.0 – 23.0) <sup>*&amp;</sup>	22.0 (17.0 – 29.0) <sup>*#</sup>	31.0 (23.0 – 47.0) <sup>*#&amp;</sup>	< 0.0001
Serum creatinine (μmol/L)	65.3 ± 15.5	68.8 ± 16.0 <sup>*&amp;</sup>	70.5 ± 16.0 <sup>*#</sup>	74.9 ± 17.2 <sup>*#&amp;</sup>	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	108.0 ± 25.4	102.5 ± 23.7 <sup>*&amp;</sup>	99.9 ± 19.6 <sup>*#</sup>	95.5 ± 19.5 <sup>*#&amp;</sup>	< 0.0001
Physical activity (MET-h/week)	24.0 (10.5 – 49.0)	24.0 (10.5 – 45.0)	23.0 (10.5 – 42.0)	21.0 (10.5 – 42.0) <sup>*</sup>	0.006
<p>1. Data were means ± SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.</p> <p>2. P for trend was calculated for the linear regression analysis tests across the groups. P values were for the ANOVA or <math>\chi^2</math> analyses across the groups.</p> <p>3. <sup>*</sup>P &lt; 0.05 compared with Quartile 1 of fatty liver index; <sup>#</sup>P &lt; 0.05 compared with Quartile 2 of fatty liver index; <sup>&amp;</sup>P &lt; 0.05 compared with Quartile 3 of fatty liver index.</p> <p>4. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyltransferase; eGFR, estimated glomerular filtration rate.</p>					

**Table 2.** Pearson's correlation and stepwise regression analysis of determinants of FLI

	r	P value	Standardized $\beta$	P value
Age (years)	0.12	< 0.0001	0.01	0.010
Sex (men=1, women=2)	-0.19	< 0.0001	-0.04	< 0.0001
BMI (kg/m <sup>2</sup> )	0.71	< 0.0001	0.30	< 0.0001
WC (cm)	0.78	< 0.0001	0.42	< 0.0001
Physical activity (MET-h/week)	-0.02	0.060	-	-
SBP (mmHg)	0.32	< 0.0001	0.01	0.006
DBP (mmHg)	0.32	< 0.0001	0.01	0.047
TG (mmol/L)	0.68	< 0.0001	0.42	< 0.0001
HDL-C (mmol/L)	-0.26	< 0.0001	-	-
LDL-C (mmol/L)	0.21	< 0.0001	0.06	< 0.0001
FPG (mmol/L)	0.22	< 0.0001	-	-
Fasting insulin ( $\mu$ IU/ml)	0.40	< 0.0001	0.01	0.0002
ALT (U/L)	0.20	< 0.0001	0.05	< 0.0001
AST (U/L)	0.15	< 0.0001	-0.03	< 0.0001
$\gamma$ -GGT (U/L)	0.35	< 0.0001	0.16	< 0.0001
eGFR (ml/min per 1.73 m <sup>2</sup> )	-0.19	< 0.0001	-	-

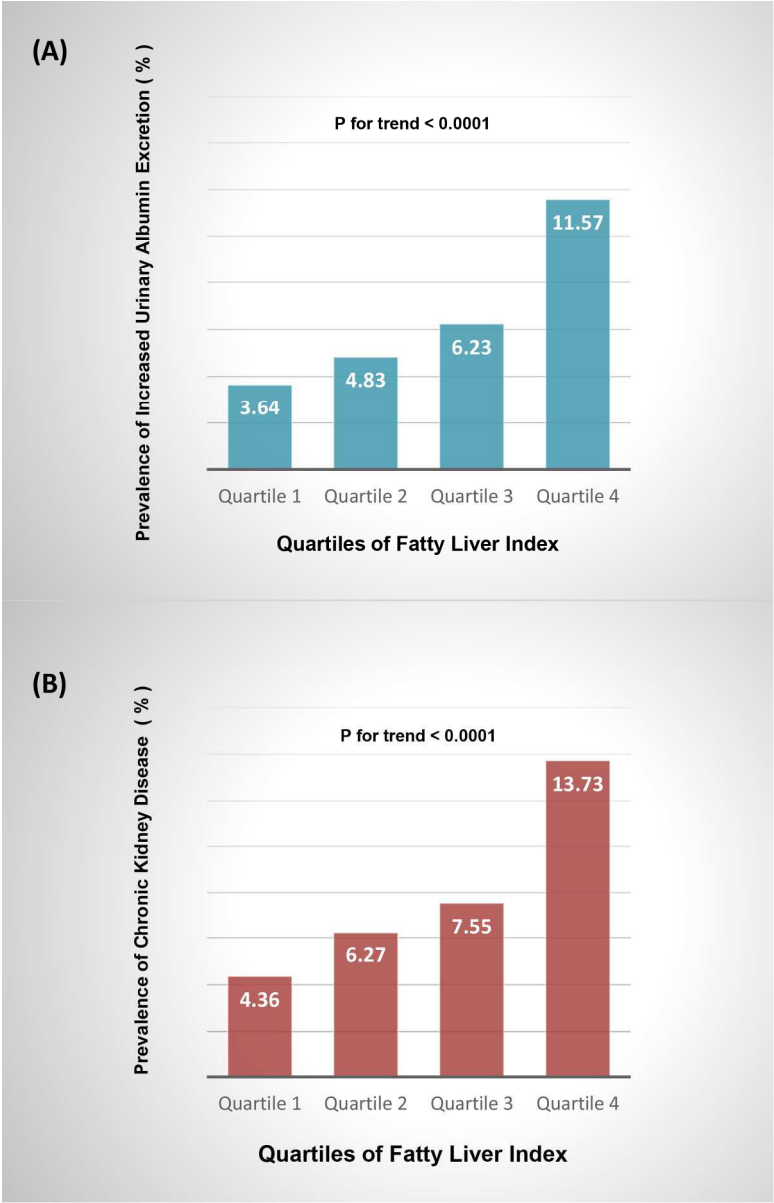
r, correlation coefficient;  $\beta$ , regression coefficient.

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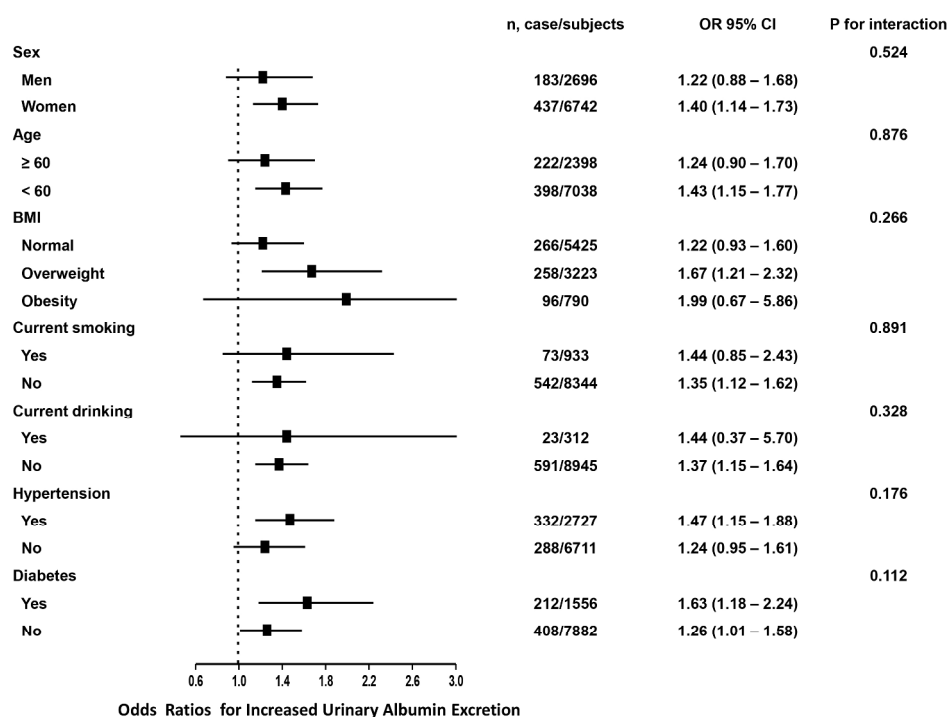
Table 3. The risk of prevalent albuminuria and CKD according to quartiles of FLI						
Increased urinary albumin excretion		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
	Model 1	1	1.34 (1.01 – 1.79)	1.76 (1.34 – 2.31)	3.46 (2.70 – 4.44)	< 0.0001
	Model 2	1	1.29 (0.97 – 1.72)	1.66 (1.27 – 2.19)	3.25 (2.53 – 4.17)	< 0.0001
	Model 3	1	0.94 (0.66 – 1.33)	1.13 (0.81 – 1.59)	2.22 (1.60 – 3.07)	< 0.0001
	Model 4	1	0.96 (0.66 – 1.39)	1.17 (0.77 – 1.77)	2.30 (1.36 – 3.90)	0.001
CKD	Model 1	1	1.47 (1.13 – 1.90)	1.79 (1.39 – 2.30)	3.49 (2.77 – 4.39)	< 0.0001
	Model 2	1	1.39 (1.07 – 1.80)	1.65 (1.28 – 2.12)	3.16 (2.51 – 3.99)	< 0.0001
	Model 3	1	0.99 (0.73 – 1.36)	1.03 (0.75 – 1.40)	1.95 (1.44 – 2.64)	< 0.0001
	Model 4	1	1.00 (0.71 – 1.40)	1.03 (0.70 – 1.51)	1.93 (1.18 – 3.15)	0.012
Data are odds ratios (95% confidence interval). Participants without increased urinary albumin excretion or CKD are defined as 0 and with increased urinary albumin excretion or CKD as 1. Model 1 is unadjusted. Model 2 is adjusted for age. Model 3 is adjusted for age, sex, current smoking status, current drinking status, physical activity, SBP, DBP, LDL-C, fasting insulin, ALT and AST. Model 4 is adjusted for age, sex, BMI, WC, current smoking status, current drinking status, physical activity, SBP, DBP, TG, LDL-C, fasting insulin, ALT,						

AST and  $\gamma$ -GGT.

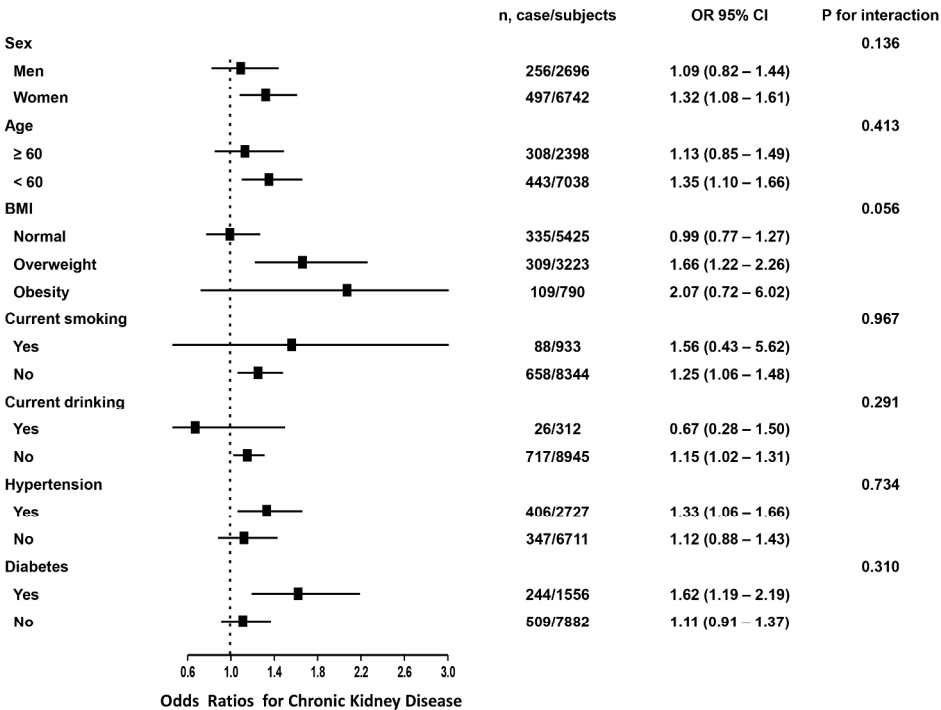
For peer review only



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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	L 1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	L 67-91
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	L 105-137
Objectives	3	State specific objectives, including any prespecified hypotheses	L 130-137
Methods			
Study design	4	Present key elements of study design early in the paper	L 141-146
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	L 141-179
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	L 141-153
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	L 155-207
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	L 193-207
Bias	9	Describe any efforts to address potential sources of bias	L 227-242
Study size	10	Explain how the study size was arrived at	L 143-146
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	L 210-219
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	L 210-242
		(b) Describe any methods used to examine subgroups and interactions	L 236-239
		(c) Explain how missing data were addressed	N.A.
		(d) If applicable, describe analytical methods taking account of sampling strategy	N.A.
		(e) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	L 248-256
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	L 248-262
		(b) Indicate number of participants with missing data for each variable of	L 248-

		interest	292
Outcome data	15*	Report numbers of outcome events or summary measures	L 264-283
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	L 264-283
		(b) Report category boundaries when continuous variables were categorized	L 210-219
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	L 285-292
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	L 295-303
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	L 374-403
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	L 329-373
Generalisability	21	Discuss the generalisability (external validity) of the study results	L 377-381
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	L 47-59

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).